Annual report 2011

Contributing to the quality of HIV care

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001. Based in Amsterdam, SHM was appointed by the Dutch Minister of Health, Welfare and Sport as the executive organisation for the registration and monitoring of HIV-infected patients in the Netherlands.

Our Mission:

To further the knowledge and understanding of the epidemiology and the course of treated and untreated HIV infection.

www.hiv-monitoring.nl

HIV Monitoring

Colophon

Annual report 2011, approved by the Board of Governors of the Stichting HIV Monitoring on 16 April 2012.

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Foreword

Over the past year, Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, has made an important and necessary contribution to the health care of those with HIV in the Netherlands through collecting, analysing and reporting data. Our work contributes significantly to the knowledge of HIV and enables physicians to assess and improve patient care. Quality of HIV care remains one of the main focal points of the foundation. During 2011, SHM continued to implement its Quality of Care programme, including registration and monitoring of the stage of HIV infection at diagnosis and the monitoring of changes in CD4 cell counts, viral load, and clinical signs and symptoms over time both following diagnosis and prior to initiation of combination antiretroviral therapy (cART). In addition, the programme encompasses the registration and monitoring of the timely start and subsequent effect of cART, including viral suppression, therapeutic failure and resistance, as well as immunological success and failure.

Part of SHM's Quality of Care programme relates to the monitoring of mortality rates and the incidence of AIDS amongst HIV-infected individuals. These figures have declined steadily since the introduction of cART, as has the proportion of patients dying of AIDS. However, the incidence of renal disease, osteoporosis and non-AIDS malignancies, as well as the incidence of death from other causes, is rising. These trends are largely the result of successful treatment of HIV in infected patients, which has led to an increasing proportion of patients with high CD4-cell counts. Not only demographic features, but also co-infections, HIV and antiretroviral treatment itself, contribute to the incidence of individual non-AIDS-defining serious diseases. The incidence of non-AIDS-defining malignancies, diabetes mellitus, myocardial infarction, osteoporosis and stroke is higher in HIV-positive patients on cART than in age- and gender-matched individuals in the general population of the Netherlands. Because the HIV population is ageing and serious non-AIDS-defining diseases in the general population occur at a higher rate with increasing age, it is to be expected that the incidence of certain non-AIDS-defining diseases will continue to increase in the future.

The trends highlight the need for regular and careful monitoring of the health of HIV-positive patients. This is particularly true as more patients live with HIV and take antiretroviral medication in the long term. Further study is needed to determine the extent to which exposure to long-term cART, HIV viraemia, inflammatory responses and immune system activation contribute to non-AIDS-related morbidity and mortality.

The infrastructure created by SHM, in collaboration with the network of HIV treatment centres, for the collection, quality control and analysis of data is easily adapted to other infections and has been successfully implemented for hepatitis B (HBV) and hepatitis C (HCV) co-infections. Monitoring of chronic HBV and HCV is currently performed by SHM for the HIV co-infected population. Monitoring of HBV and HCV is also possible for non-HIV-infected patients. Although treatment of HBV and HCV is not yet optimal, direct-acting antiviral drugs exist for HBV and have recently become available for HCV. Monitoring these infections and their response to treatment should provide useful insights into the management of chronic infections.

During 2011, SHM continued to study sexual networks for the transmission of HIV by comparing nucleotide sequences of the HIV pol gene. These sequences are obtained from patients to determine viral resistance to particular therapies. Comparing these sequences provides an indication of transmission chains and may give better insight in changes in the course of the epidemic. Together with the Department of Infectious Disease Epidemiology at Imperial College in London, the Department of Experimental Immunology at the Academic Medical Centre in Amsterdam and the Sanger Institute in Cambridge (UK), SHM is planning a further study aimed at understanding changes in HIV characteristics over time.

In the foundation's Monitoring Report 2011 - Human Immunodeficiency Virus Infection in the Netherlands, published on World AIDS Day, 1 December 2011, we reported that the trends were best characterised as 'cautiously optimistic'. The report provides a comprehensive review of trends over time in the HIV epidemic and the effect of treatment on HIV infection up to 30 June 2011. The 2011 Annual Report presents, in addition to organisational and financial information, updated data on the monitoring of HIV through to the end of 2011. I am happy to report that the data compiled so far of 894 new registered HIV diagnoses for calendar year 2011 supports the trends we noted in the monitoring report of no further increase in the number of diagnoses annually. We will continue to monitor these trends during 2012 and provide a further update in our Monitoring Report 2012.

SHM is structurally supported by the Netherlands Ministry of Health, Welfare and Sport. The Dutch government in this way acknowledges the importance of a national monitoring system for HIV and AIDS, and it contributes substantially to the knowledge of the effect of lifelong treatment of HIV on survival and morbidity and on the course of the HIV/AIDS epidemic in the Netherlands and in other Western countries.

The Netherlands is the only country in the world with a framework for systematically collecting HIV data for the long-term follow-up of all registered HIV-infected patients. This places us in a unique and enviable position and allows us, together with the HIV treatment teams from the 25 HIV treatment centres, to aspire to the highest standard of HIV care.

In closing, I would like to recognize the contribution of both professionals and patients. SHM is very grateful to the many people working in the HIV treatment centres for their ongoing hard work and support. Our monitoring approach would not be possible without their involvement. I must also thank the patients living with HIV for their cooperation in providing their data as their data is key to what we do. Finally, I would like to thank the board and the SHM staff for their dedication and commitment.

Prof. Frank de Wolf MD

Director

Amsterdam, 16 April 2012

Letter from the Board Chair

Stichting HIV Monitoring (SHM) contributes significantly to the quality of care of HIV-infected people throughout the Netherlands. Through life-long treatment, HIV has become a chronic disease in an expanding group of people who are surviving longer with the infection. Currently, approximately 15,000 HIV-infected people are in care in the Netherlands, and 1200 persons with new diagnoses are registered per year. Optimal treatment of the HIV-infected individual benefits not only the individual but also slows down the epidemic. On the other hand, suboptimal treatment could have serious implications, such as the subsequent development of HIV resistance. Through continuous monitoring of HIV and its treatment, these threats to individually infected patients and to public health can be uncovered in time, and health care and prevention measures can be established before the need becomes critical.

HIV patient care in the Netherlands is currently concentrated in 18 general and 8 academic hospitals. In 2001, the Health Council of the Netherlands, the independent scientific advisory body to Government and Parliament, recommended such a concentration of care based on the Ministry of Health, Welfare and Sport's acknowledgement of these hospitals as specialised HIV treatment centres or subcentres. Such acknowledgement was, and still is, conditioned by a series of organisational and professional requirements to ensure the high quality of individual HIV care. At the same time, designating specific hospitals as HIV treatment (sub)centres would enable efficient monitoring of changes in the course of the HIV epidemic.

In 2007, a critical assessment of the quality of care for HIV-infected patients at each HIV treatment centre and subcentre was initiated by the Dutch Association of Physicians in AIDS (NVAB, currently known as the Dutch Association of HIV-treating Physicians, the NVHB). SHM played an essential role in providing and analysing the data for this assessment and for the resulting report, which was published in April, 2011 by the NVHB. The conclusions drawn from the analysis are positive and indicate that the quality of HIV care in the Netherlands is of a consistently high standard, which is reflected in the various HIV treatment centres throughout the country. The Quality Commission from the NVHB has recommended that this inspection be repeated in 2 to 3 years. SHM will undoubtedly be involved in this and any further evaluations.

The results of the assessment by the NVHB and SHM were useful contributions to the programme Visible Care (Zichtbare Zorg, ZiZo) run by the Health Care Inspectorate and commissioned by the Ministry of Health, Welfare and Sport. ZiZo's aim is to compare quality of care in the health care sector. In 2010 and 2011, SHM was involved in the HIV working group of ZiZo and contributed to developing quality indicators that provide insight into HIV care. SHM also carried out a pilot study to test these quality indicators and then assisted in the roll-out to all HIV treatment centres. Results of the 2011 ZiZo quality of care survey that used data from 2009 and 2010 confirmed the results of the assessment by the NVHB.

In 2011, SHM made further progress on the demographic reports that will be available for each HIV treatment centre starting mid-2012. Essentially, there are two sets of reports: a centre-specific set that gives each treatment centre an overview of the developments and trends of their own treatment population in comparison to the national total and a second set that provides a real-time update per individual patient for the treating physician. By providing these reports, SHM is improving the quality of service to teams at HIV treatment centres by providing easier access to information directly relevant to their patients and patient groups.

As many of you are aware, the landscape of health care is changing drastically. In particular, the organisation and financing of HIV care is expected to undergo substantial changes as of 2013. Despite these changes, it is essential that the high quality of HIV care in the Netherlands is maintained. To ensure this, it is proposed that the quality of HIV care be regulated via certification of HIV care by the NVHB. As part of this proposal, certified HIV care facilities would be asked to deliver their data to SHM in connection with maintaining the quality of HIV care and the continued monitoring of the epidemic.

In addition to SHM's contribution to the quality of HIV care, it also makes an important scientific contribution to HIV research both nationally and internationally. Research conducted by SHM results in tangible advice for medical professionals, as well as for patients, government and the health care sector at large.

Finally, I would like to thank all the SHM employees for their dedication and hard work and all health professionals and patients for their continued support. Through the ongoing collection and analysis of data, I trust that we can continue to add to the knowledge of HIV care and treatment.

Dr. Frank Kroon

Chairman of the Governing Board

Amsterdam, 16 April 2012

Overview

Quality data collection

Over the past 10 years, SHM has developed significant expertise in collecting and processing high-quality data from patients with HIV, a process we continued to refine in 2011. Continuous collection of data is essential for the work of SHM and is carried out at 25 HIV treatment centres and subcentres and at 4 paediatric HIV centres in the Netherlands.

In 2011, the steps initiated in 2010 to improve the information and communications technology (ICT) infrastructure and data management processes were continued. This included improvements in the data warehouse, patient reports and further automation of the importation of data. In addition to these improvements, a number of data products were developed.

Trends in the epidemic and treatment during 2011

The number of people living with HIV infection continues to increase in the Netherlands. As of 31 December 2011, within the Dutch national HIV registration and monitoring database, known as the ATHENA cohort, SHM registered a total of 19,752 persons diagnosed with HIV. Of that total, 1,372 persons were first registered in 2011, and 61% of the 1,372 were diagnosed with HIV infection in 2011. At the end of 2011, the total of registered HIV-infected children (less than 18 years of age) was 202. During 2011, five HIV diagnoses were made in this age group. Almost one third of the population in care was 50 years of age or older.

HIV in the Netherlands continues to be a concentrated epidemic amongst men who have sex with men (MSM). In 2011, 79% of the adult patients who were registered and being monitored in the Netherlands were male, and many of these became infected through homosexual contact. However, the results published in our scientific report for 2011 are confirmed, showing accumulating evidence that the increasing trend in the number of new diagnoses amongst MSM has halted.

Over time, patients with HIV have begun to be diagnosed at an earlier stage of infection with higher CD4-cell counts, indicating a less impaired immune system. Half of the population in 1996 had CD4-cell counts of 250 cells/mm^3 or higher at the time of diagnosis, whereas half the population in 2011 had 350 cells/mm^3 or higher.

In 2011, 85% of HIV-infected adults were on combination antiretroviral therapy (cART), and 14% were not being treated, mainly because they did not meet the criteria for starting cART or their treatment status was not yet registered. The most frequent combination of drugs at the start of HIV treatment included tenofovir and emtricitabine combined with efavirenz or ritonavir-boosted darunavir.

Hepatitis B (HBV) and C (HCV) infection are highly prevalent amongst HIV-infected individuals and are associated with major liver diseases. In 2011, chronic infection with HBV was found in 8% of HIV-infected patients who were tested, and chronic infection with

HCV was present in 12%. Co-infection with both HBV and HCV was diagnosed in 1%. Of the HBV co-infected patients, liver fibrosis developed in 13% and cirrhosis in 7%; hepatocellular carcinoma was diagnosed in 1%. For the HCV co-infected patients, 19% had liver fibrosis, 8% cirrhosis, and 1% hepatocellular carcinoma. The risk of liver disease in HIV-positive patients with a co-infection was higher than in a comparable group without a co-infection.

Mortality and AIDS incidence rates have dropped since 1996 compared to the period before the introduction of cART, but mortality rates are still higher when compared with the gender- and age-matched general population. AIDS still occurs, with a stable number of 250 to 300 new diagnoses per year.

"Monitoring Report 2011 – HIV Infection in the Netherlands"

On World AIDS Day, 1 December 2011, SHM published its annual monitoring report that presented major developments in the effects of treatment on the course of HIV infection and the epidemic in the Netherlands, with information extending back to 1996.

The 2011 monitoring report described some encouraging trends. It reported that a larger number of individuals registered with HIV are receiving cART, with a larger proportion reaching viral suppression to a level below the assay threshold for a longer period of time and experiencing CD4-cell increases higher than ever before. Moreover, it was reported that there appears to be no further increase in the annual number of new HIV diagnoses.

Quality of care

In relation to the Visible Care programme (Zichtbare Zorg, ZiZo), run by the Public Health Inspection Agency as commissioned by the Ministry of Health, Welfare and Sport, SHM has contributed to the development of quality indicators providing insight into HIV care. SHM also carried out a pilot study to test these quality indicators and then assisted in rolling out these quality indicators to all HIV treatment centres.

In addition to the activities for ZiZo, in 2011 SHM continued to develop its Quality of Care programme looking at the influence of HIV quality of care on the outcome of treatment and disease progression.

An area of focus in the programme is the timely start of therapy in patients who enter into care at an HIV treatment centre at an early stage of infection. In 2009 and 2010, 6% of the patients who presented with more than 350 CD4 cells/mm^3 were started on therapy with less than 200 CD4 cells/mm^3. The rate of CD4-cell decline after entry into care is crucial for the timely start of treatment. Consequently, the frequency of monitoring is an important factor in preventing the late start of treatment. Frequency of monitoring is also important after the start of treatment because it plays a large role in the early recognition of treatment failure and in avoidance of prolonged exposure to high concentrations of HIV or the development of resistance. It also enables patients to change sooner to a more suitable treatment combination. Through the Quality of Care programme, SHM will help to determine the optimal frequency for monitoring patients.

Scientific output

In addition to its yearly monitoring report, SHM's contribution to the knowledge and understanding of the HIV/AIDS epidemic and the effect of antiretroviral treatment on the course of HIV infection is visible in its scientific output. In 2011, SHM was involved in 41 publications in peer-reviewed international scientific journals and in 39 presentations at international peer-reviewed conferences, workshops, and meetings.

NCHIV 2011

SHM's work was also presented at the 2011 National Conference on HIV Pathogenesis, Prevention and Treatment (NCHIV). This yearly conference is organised by SHM in collaboration with the AIDS Fund, the Academic Medical Center of the University of Amsterdam (AMC-UvA) (including the Laboratory of Viral Immune Pathogenesis of the Department of Experimental Immunology [LVIP], the Department of Global Health, and the Amsterdam Institute for Global Health and Development [AIGHD]), the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment (CIb-RIVM), the Sanquin Blood Supply Foundation, and the Dutch Association of HIV-Treating Physicians (NVHB).

Collaborations

SHM maintains a strong collaboration with all HIV treatment centres in the Netherlands. The HIV treating physicians, together with data collection staff in HIV treatment centres, are crucial for the work of SHM.

SHM continues to collaborate with other observational cohorts both within and outside Europe. Within the Netherlands, we have an agreement with the CIb-RIVM for the exchange of data collected through SHM for purposes of surveillance that is carried out by the CIb-RIVM. SHM also collaborates with the AMC-UvA and the Public Health Service (GGD) in Amsterdam on various projects including the national Co-morbidity and Aging with HIV study and the Amsterdam Cohort Studies. In 2011, SHM also collaborated with the NVHB on the "Quality of HIV Care in the Netherlands" report, and was a member of the Visible Care (ZiZo) HIV working group.

Internationally, SHM collaborates with other research groups and observational cohorts in Europe, the United States, and Canada. SHM is involved in international collaborations including A Collaboration on HIV-2 Infection ($ACHI_{E}V_{2E}$), the Antiretroviral Therapy Cohort Collaboration (ART-CC), the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE), the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study, and the Department of Infectious Disease Epidemiology (DIDE) at the Imperial College in London, UK. Other collaborations include the European Centre of Disease Prevention and Control (ECDC), EuroSIDA, the HIV Cohorts Analyzed Using Structural Approaches to Longitudinal Data (HIV-CAUSAL) collaboration, HIV in Europe, and the HIV Resistance Response Database Initiative (RDI). The European Coordinating Committee for the Integration of Ongoing Coordination Actions Related to Clinical and Epidemiological HIV

Research (EuroCoord) is another collaboration. In 2011, EuroCoord's governing body, the Council of Partners, was chaired by Frank de Wolf, Director, SHM.

PhD programmes

In 2011, the topics of three ongoing PhD programmes were the clinical implications of immune deficiency and restoration during treatment for HIV infection, the consequences of episodes of HIV viraemia on the clinical outcome of treatment of HIV, and the effect of cART on HIV-infected individuals treated in Curaçao compared to that on infected patients from the Netherlands Antilles treated in the Netherlands. Two of these PhD programmes are expected to be completed in 2012.

Organisational report

HIV treatment centres

The monitoring of HIV-infected adults is a collaborative effort involving Stichting HIV Monitoring (SHM) and a total of 25 health institutes that are acknowledged by the Dutch Minister of Health, Welfare and Sport as HIV treatment centres or subcentres. In addition, HIV-infected children and adolescents are monitored in four institutes that are recognized as paediatric HIV treatment centres.

In 2011 the following health institutes were involved as (sub)centres for adult HIV care (in alphabetical order of town):

1	Medisch Centrum Alkmaar	Alkmaar
2	Flevoziekenhuis	Almere
3	Academic Medical Centre of the University of Amsterdam	Amsterdam
4	Onze Lieve Vrouwe Gasthuis	Amsterdam
5	Sint Lucas Andreas Ziekenhuis	Amsterdam
6	Slotervaartziekenhuis	Amsterdam
7	Stichting Medisch Centrum Jan van Goyen	Amsterdam
8	VU Medisch Centrum	Amsterdam
9	Rijnstate Arnhem	Arnhem
10	HagaZiekenhuis (location Leyweg)	Den Haag
11	Medisch Centrum Haaglanden (location Westeinde)	Den Haag
12	Catharina Ziekenhuis	Eindhoven
13	Medisch Spectrum Twente	Enschede
14	Universitair Medisch Centrum Groningen	Groningen
15	Kennemer Gasthuis	Haarlem
16	Medisch Centrum Leeuwarden	Leeuwarden
17	Leids Universitair Medisch Centrum	Leiden
18	Academisch Ziekenhuis Maastricht	Maastricht
19	Universitair Medisch Centrum Sint Radboud	Nijmegen
20	Erasmus Medisch Centrum	Rotterdam
21	Maasstad Ziekenhuis	Rotterdam
22	St. Elisabeth Ziekenhuis	Tilburg
23	Universitair Medisch Centrum Utrecht	Utrecht
24	Admiraal De Ruyter Ziekenhuis	Vlissingen
25	Isala Klinieken (location Sophia)	Zwolle

Centres for the treatment and monitoring of paediatric HIV and AIDS were:

A	Emma Kinderziekenhuis, AMC-UvA	Amsterdam
B	Beatrix Kinderziekenhuis, UMCG	Groningen
C	Erasmus MC - Sophia	Rotterdam
D	Wilhelmina Kinderziekenhuis, UMCU	Utrecht

SHM has contracts with each centre or subcentre for the collection of demographic, epidemiologic, clinical, virologic, immunologic, and pharmacologic data for HIV-infected patients who are being followed in one of these hospitals. These contracts are automatically renewed every three years.

In addition to its work in the Netherlands, SHM, in collaboration with the Red Cross Blood Bank in Willemstad, Curaçao, also collects the data of HIV-infected persons who are seen by HIV/AIDS doctors at the St. Elisabeth Hospital in Curaçao.

Internal organisation SHM

The Director of Stichting HIV Monitoring, Frank de Wolf, is responsible for the day-to-day management of SHM's activities. There are two units for SHM's primary activities: one for the collection of patient data and quality control and the other for data processing and analysis, along with one supporting unit.

The SHM's data collectors are employed in the patient data and quality control unit. This unit includes administering patient registration, which involves the inclusion and exclusion of data and assignment of an anonymous identification code to each patient. The data monitors, who are responsible for the execution of the data quality control procedures, are also part of this unit.

The patient data and quality control unit coordinates the data management. This function is outsourced to the Clinical Research Unit, Department of Clinical Epidemiology and Biostatistics from the Academic Medical Center of the University of Amsterdam. At least twice a year, in February/March and in June/July, data from the database are merged into a dataset to be used for data processing and analysis. The patient data and quality control unit is managed by Sima Zaheri. During 2011, the average number of fte's in the unit was 18.03.

Five researchers in the field of epidemiology, statistics, mathematical modelling of HIV, and modelling transmission networks staff the data processing and analysis unit. Together, they execute the HIV registration programme, the results of which are presented in the annual SHM Monitoring Report published on World AIDS Day, as well as in separate publications in peer-reviewed international scientific journals. This unit supports and collaborates nationally with researchers in HIV treatment centres and internationally with research groups working with comparable observational cohorts in the field of epidemiology and the treatment of HIV. Also, this unit arranges for support of research applications from the Dutch pharmaceutical industry.

In addition to the five researchers, the unit had two assistant researchers in two PhD programmes during 2011. These programmes focus on the study of clinical implications of immune deficiency and restoration during treatment for HIV infection and on the consequences of episodes of HIV viraemia on the clinical outcome of treatment of HIV. In addition, the unit continues to support a third PhD programme that compares the effect of cART on HIV-infected individuals treated in Curaçao with that on infected patients from the Netherlands Antilles treated in the Netherlands.

In 2011, an average of 5.50 fte's was assigned to the data processing and analysis unit, which is led by Frank de Wolf (1.00 fte), Director of SHM.

The primary activities of SHM are supported by the members of the office staff, which includes the secretariat, financial and personnel administration, internal controlling, and communication. It is supervised by SHM's controller, Danielle de Boer, with an average of 3.97 fte's assigned in 2011. This number has remained constant over past years.

As of 31 December 2011, SHM had an average total of 19.69 fte's. In addition, SHM covers the costs for a total of 12.50 fte's who are appointed in the HIV treatment centres to handle data collection and entry, but who are not on the staff of SHM. The average sick leave during 2011 was 3.09%, which was 1.79% less than in 2010.

Database & data management

In 2011, Stichting HIV Monitoring (SHM) continued the steps initiated in 2010 to improve the information and communications technology (ICT) infrastructure and data management processes:

- **Data warehouse:**
  Data from different sources were merged and imported into SHM's data warehouse during 2011. This resulted in 160 tables and 159,079,711 records that are available in real time for data analysis and for presentation of data to the treatment centres in table and report form.

- **Patient reports, graphs:**
  Since 2003 patient charts and graphs, which are used in the HIV treatment centres for discussions and presentations, have been generated in Microsoft Access databases that can be downloaded from a secure website. These hospital-specific data sets are updated overnight and are then accessible to the treatment centres. Due to the continuous growth of data, the time taken to download data sets has increased significantly, making Microsoft Access inadequate for this purpose. In 2011 a new reporting tool, Microsoft Report Builder, was chosen. This software has the advantage that reports, charts and data queries can be generated directly and securely online from the tables in the SHM data warehouse and then presented to the HIV treatment centres. In 2011 SHM's reporting server was set up in collaboration with the Clinical Research Unit (CRU) of the Academic Medical Center (AMC) at the University of Amsterdam (UvA). Standard patient reports, custom reports, graphs and standard data queries were re-evaluated and built into Microsoft Report Builder. These reports will be presented to all centres during 2012, and users will be trained in their use in daily work.

- **Standardisation of 'Lab-Link':**
  In 2011 work started on standardising Lab-Link, the automated link that allows laboratory data from various computer systems in the HIV treatment centres to be entered directly and anonymously into the SHM database. In collaboration with the AMC's CRU and General Service ICT (ADICT), a standard protocol was developed for sending laboratory results as HL7 messages (an international standard for electronic data exchange between health care information systems) from a server at an HIV treatment centre via a secure connection to a Cloverleaf server in the AMC. In collaboration with ADICT, a procedure was developed to modify the HL7 messages received from the treatment centres so that they are transferred one by one to another server (a Mirth server) in the AMC. On the Mirth server, the HL7 messages are converted to laboratory results that can be imported into the SHM data warehouse tables. The treatment centres that send their data via Lab-Link (St Elisabeth Ziekenhuis, Tilburg, the Slotervaartziekenhuis, Amsterdam, the Medisch Spectrum Twente, Enschede, the Leids Universitair Medisch Centrum, Leiden, the Maasstad Ziekenhuis, Rotterdam, the Universiteit Medisch Centrum Utrecht and the

Isala Klinieken (Sophia), Zwolle) were approached in 2011 and asked to participate in the standardisation process. In the AMC an internal connection transfers the results from the laboratory system directly to the Mirth server. A Lab-Link mapping tool has been developed by the CRU in Microsoft Access, which receives and standardises laboratory results from different treatment centres with different terminology, and in 2011, 1,179 unique laboratory terms were standardised.

In addition to the treatment centres listed above, in two other centres, the Academisch Ziekenhuis Maastricht and the Medisch Centrum Alkmaar, the possible use of Lab-Link has been investigated, and the necessary preparations have been started.

- **Standardisation of import databases:**
  Until 2003, data from patients was collected in local Access databases (HIVREG) and merged every six months. In 2003, an Oracle Clinical database for centralized data collection via a secure Internet connection was implemented. To date, the data from these two types of databases with different formats have been synchronized and merged. Data corrections resulting from data quality controls have then been entered into both systems. In 2010, a standardisation process was begun, with the aim of using the Oracle Clinical database as the principle database for manual data entry and corrections. In 2011, the implementation of these processes was continued; the importing of data was tested, and any problems were identified and remedied. In 2012, the implementation of the data importation will be finalized.

In addition to these improvements in data management structure in 2011, a number of data products were developed:

- **Centre-Specific (CS) reports:**
  On SHM's website, standard reports have been developed, with the goal of providing treatment groups with an overview of the developments, trends and issues within their own patient population every six months. This data product will be tested in 2012 by a clinicians' panel, which had already reached agreement on the content and form of presentation in 2010. After testing, these CS reports will be presented to all HIV treatment centres nationally.

- **Data sets for collaborative projects:**
  In 2011, data sets from the SHM data warehouse were developed as tables for three national collaborative projects: the Co-morbidity and Ageing with HIV project, the Mosaic study and ZiZo (Zichtbare Zorg, Visible Care). Also, data management activities have been carried out and data sets created for two international collaborations, the D:A:D study and COHERE.

Volume of data collection

The results of the data collection are summarised in *Table 1*. The total volume of data increased in 2011 by 83% in comparison to 2010. This can be explained by the increased growth of the automated data collection by Lab-Link, which increased in 2011 by 700%. This dramatic increase is due to the improvement in the Lab-Link data quality, with retrospective data for all years retrieved and imported into the SHM data warehouse for two centres, AMC, Amsterdam and St Elisabeth Ziekenhuis, Tilburg. The volume of manual data collection increased in 2011 by 6%, which is lower than the increase in 2010 and can be explained by the slower increase in the number of data points collected for HIV-infected adults, HIV-exposed children and pregnancies. The slower increase is a result of reducing the data backlog from 2010, which were mainly data points collected for baseline and follow-up data.

Table 2 shows the percentage of patients with delays in data collection (data backlog) at each HIV treatment centre. A distinction is made between an estimated backlog of more than 365 days and one of less than 365 days. The estimated data backlog is based on the difference between the predicted time and the actual time between the most recent patient visit and the following visit. The predicted time is calculated based on the frequency of visits during the previous year and the last visit. A difference of 180 days or less is not considered a delay.

In 2011, the long-term backlog in data collection decreased by 2% compared to 2010. This is largely due to the ongoing training of data collectors in efficiently organising the logistics of data collection, so that the follow-up data of patients with the largest data-entry backlog takes priority. The long-term backlog at the Academisch Ziekenhuis Maastricht has been reduced through the placement of SHM data collectors who have supported the local data collectors.

The short-term data collection backlog decreased 7% in 2011, which is a result of the accurate monitoring of data-entry delays by data collectors and data monitors.

Quality control (QC)

In 2011, priority was given to controlling data in the SHM data warehouse from various sources. Validation checks were performed on individual records. All records in the data warehouse were compared with the original source databases. Procedures for validation of Lab-Link data were also considered. Lab-Link data from the AMC, Amsterdam and St Elisabeth Ziekenhuis, Tilburg were retrospectively retrieved and fully re-imported.

Baseline data was checked for 81 randomly selected patients. The controlling of data related to cause of death and co-morbidity, defined as “endpoints”, continued to be controlled in 100% of the cases in 2011 and were also classified for data analysis.

As part of the individual coaching programme for the 44 data collectors, an average of four patient files of each data collector was selected for quality control. The results of the quality control were discussed with the responsible data collectors, and item-specific training was given.

Table 1: Data collection results 2004–2011

	2011	2010
Manual data collection		
HIV infected adults		
Baseline	258,734	186,507
Follow-up	5,779,482	6,044,689
End of follow-up	11,996	11,680
Laboratory results	8,690,310	8,166,082
Subtotal (data points)	14,740,522	14,408,958
HIV infected children		
Baseline	4,271	944
Follow-up	174,232	80,126
End of follow-up	783	195
Laboratory results	478,313	104,370
Subtotal (data points)	657,599	185,635
HIV exposed children		
Baseline	2,893	2,040
Follow-up	14,401	11,243
End of follow-up	1,549	1,069
Laboratory results	19,331	11,407
Subtotal (data points)	38,174	25,759
Pregnancies		
Baseline	5,020	2,682
Follow-up and end of pregnancies	16,684	8,816
Laboratory results	12,138	7,632
Subtotal (data points)	33,842	19,130
Additional data		
Causes of death (numbers)	185	152
Cardiovascular disease (numbers)	223	219
Other co-morbidities (numbers)	194	199
Subtotal additional data (numbers)	602	570
Total manual collection (data points)	**15,470,739**	**14,640,052**
Increase (%) manually collected data (data points)	**6%**	**12%**
Automated data collection		
Number of lab results per year	3,612,404	433,254
Total automated collection (estimated data points)	**14,449,616**	**1,733,016**
% Lab-Link from total lab results	61%	9%
Increase (%) Lab-Link data	**700%**	**11%**
Total data collection (data points)	**29,920,355**	**16,373,068**
Increase (%) total data	**83%**	**12%**
Number of patients in follow-up	16,223	14,877
Increase (%) patients in follow-up	**9%**	**5%**

2009	2008	2007	2006	2005	2004
78,396	69,364	53,359	56,700	64,062	126,924
4,941,270	4,824,298	4,316,778	3,615,436	3,325,594	2,575,088
11,123	9,778	11,561	13,043	8,691	7,799
7,637,999	6,833,090	7,124,209	7,112,151	5,961,439	5,760,663
12,668,788	11,736,530	11,505,907	10,797,330	9,359,786	8,470,474
1,976	688	1,051	1,750	4,148	1,425
113,967	118,562	168,704	314,136	311,260	75,263
150	0	63	165	75	0
271,267	200,129	441,003	536,153	809,088	261,036
387,360	319,379	610,821	852,204	1,124,571	337,724
80	901				
4,787	2,870				
192	28,793				
2,916	15,336				
7,975	47,900				
940	1,705	1,275	3,876	3,648	0
7,548	16,044	12,020	37,216	35,540	0
5,865	14,123	10,532	42,905	31,332	0
14,353	31,872	23,827	83,997	70,520	0
113	108	128	164	27	1
167	55	81	151	108	45
529					
809	163	209	315	135	46
13,079,285	**12,135,681**	**12,140,555**	**11,733,531**	**10,554,877**	**8,808,198**
8%	**0%**	**3%**	**11%**	**20%**	
389,015	222,668	119,668	95,685		
1,556,060	**890,672**	**478,672**	**382,740**		
9%	11%	6%	5%		
75%	**86%**	**25%**			
14,635,345	**13,026,353**	**12,619,227**	**12,116,271**	**10,554,877**	**8,808,198**
16%	**3%**	**4%**	**15%**	**20%**	
14,138	13,296	11,666	10,275	9,399	8,537
6%	**14%**	**14%**	**9%**	**10%**	

Table 2: Percentage of patients being followed in each treatment centre with average data collection backlog of more than and fewer than 365 days

HIV treatment centre	Location	>365 days		<365 days	
		2011	2010	2011	2010
MCA	Alkmaar	0%	1%	0%	3%
Flevo Zkh	Almere	0%	0%	2%	30%
AMC-UvA	Amsterdam	0%	2%	7%	25%
MC Jan van Goyen	Amsterdam	0%	0%	1%	5%
OLVG	Amsterdam	0%	0%	1%	6%
St Lucas Andreas Zkh	Amsterdam	0%	0%	23%	22%
Slotervaart Zkh	Amsterdam	0%	0%	2%	14%
VUMC	Amsterdam	0%	1%	3%	25%
Rijnstate	Arnhem	0%	0%	1%	32%
Haga Zkh – Leyweg	Den Haag	0%	3%	2%	4%
MCH – Westeinde	Den Haag	0%	4%	16%	30%
Catharina Zkh	Eindhoven	0%	4%	6%	6%
MST	Enschede	5%	0%	1%	4%
UMCG	Groningen	0%	1%	45%	45%
Kennemer Gasthuis	Haarlem	0%	6%	8%	31%
MC Leeuwarden	Leeuwarden	0%	0%	8%	17%
LUMC	Leiden	1%	0%	1%	9%
AZM	Maastricht	0%	40%	19%	14%
UMC St Radboud	Nijmegen	0%	5%	15%	41%
Erasmus MC	Rotterdam	0%	5%	17%	17%
Maasstad Zkh	Rotterdam	0%	0%	18%	10%
St Elisabeth Zkh	Tilburg	0%	3%	1%	3%
UMCU	Utrecht	1%	0%	6%	3%
Admiraal de Ruyter Zkh	Vlissingen	0%	1%	9%	2%
Isala Klinieken – Sophia	Zwolle	9%	4%	4%	9%
Total		**1%**	**3%**	**9%**	**16%**

The number of verified patient files per selection procedure is summarised in *Table 3*. In 2011, data from a total of 1,090 patients were checked by SHM data monitors. Within the framework of the D:A:D study, data from 417 patients were checked for cardiovascular accidents and other co-morbidities. The causes of death for 152 patients were verified and classified. On average, each HIV treatment centre was visited 13 times during the year by the SHM data monitor(s) responsible for that centre.

The number of patients whose files were quality-controlled decreased by 41% compared to 2010. This can be explained by two factors: first, an increase in the number of selected co-morbidities and causes of death that was controlled in a more comprehensive and detailed manner and, second, more priority was given to controlling data in the SHM data warehouse at table and record level, such that no patient files needed to be consulted.

Training and education

In November 2011, a review day was organised for the data collectors that included a lecture on neurological disorders in HIV-infected patients. SHM's data monitors also discussed changes in the data structure at SHM, the collection of hepatitis B and C data and other types of data that will be collected in 2012. In addition, the data collectors were trained in procedures and activities related to collecting new types of data and maintaining data quality.

An internal training was organised for the Quality Control (QC) group, and all data monitors were intensively trained in the use of SAS® software during a two-day customised programme. Additionally, all data monitors were trained in project management and in Microsoft Project software.

In December 2011, a proportion of the data monitors were trained to recognise various infectious diseases.

Table 3: Number of patient files checked by data monitors per data selection criterion

	Number of patient files							
Selection criteria for quality checks	**2011**	**2010**	**2009**	**2008**	**2007**	**2006**	**2005**	**2004**
Random selection								
Random selection of adverse events data	0	0	0	0	2	1	0	0
Random selection of antiretroviral medication data	1	0	2	8	3	13	6	0
Random selection of baseline data	81	0	0	0	52	17	7	1
Random selection of CDC events data	0	0	0	1	2	11	0	0
Random selection of co-medication data	0	0	0	0	0	2	0	0
Random selection of all patient data	0	1	0	2	1	17	87	118
Random selection of data from last year of follow-up	0	0	0	0	0	38	126	203
Subtotal random selection	**82**	**1**	**2**	**11**	**60**	**99**	**226**	**322**
Consistency checks								
Inconsistencies in adverse events data	237	1,147	74	1,056	30	69	1	0
Inconsistencies in antiretroviral medication data	2	2	23	209	1	18	3	0
Inconsistencies in baseline data	11	0	0	116	362	97	161	0
Priority analyses baseline data	0	0	10	0	207	0	0	0
Inconsistencies in CDC event data	1	2	3	257	122	289	0	0
Inconsistencies in co-medication data	0	0	4	2	7	17	0	0
Inconsistencies in laboratory data	1	4	16	93	18	5	0	0
Subtotal consistency checks	**252**	**1,155**	**130**	**1,733**	**747**	**495**	**165**	**0**
Co-morbidity and causes of death checks								
Pregnancies	0	0	0	1	0	129	10	0
Total cardiovascular disease:	223	219	167	55	92	151	108	45
Myocardial infarction	*38*	*46*	*36*	*16*	*17*	*31*	*33*	*14*
Invasive cardiovascular procedures	*49*	*49*	*43*	*14*	*10*	*40*	*16*	*10*
Diabetes mellitus	*76*	*101*	*62*	*19*	*40*	*55*	*37*	*16*
Stroke	*60*	*23*	*26*	*6*	*25*	*25*	*22*	*5*
Chronic liver disease	23	10	22					
End stage renal disease	34	12	13					
Non-AIDS defining malignancy	137	177	381					
Causes of death in 100% of cases	185	152	113	108	128	164	27	1
Subtotal co-morbidity and cases of death checks	**602**	**570**	**696**	**164**	**220**	**444**	**145**	**46**
Subtotal personal coaching of data collectors	154	124	114	241	268	216	0	0
Total number of patient files checked	**1,090**	**1,850**	**942**	**2,149**	**1,295**	**1,254**	**536**	**368**
% change per year	**-41%**	**96%**	**-56%**	**66%**	**3%**	**179%**	**19%**	

Monitoring report

Development in the number of registered and monitored persons with HIV

By the end of 2011, a cumulative total of 19,752 patients with HIV infection were registered through the HIV treatment centres *(Table 4)* by SHM, an increase of 1,372 (7%) in comparison to 2010. AIDS developed in a cumulative total of 5,209 (26%) patients, and 1,913 (10%) died; of those, 1,790 died before 2011 and 123 in 2011.

All together, 2,216 (11%) patients were recorded as lost to follow-up, because no data were obtained on these patients in 2011. This number was reduced compared to 2010. The distribution of patients lost to follow-up amongst the HIV treatment centres indicates that the delays in data entry reported last year have been eliminated.

The number of patients actively monitored through the end of 2011 rose to 15,777, an increase of 9% in comparison to 2010. Of the 1,365 new patients registered with HIV between 1 January 2011 and 1 January 2012, 179 (13%) were diagnosed with AIDS, and 14 (1%) died *(Table 5)*.

As of 31 December 2011, data from a total of 766 HIV-infected persons, including 16 children, who were monitored at the Sint Elisabeth Hospital in Willemstad, Curaçao, were included in the SHM database. This is an increase of 64 persons compared to the number in 2010.

As of 31 December 2011, out of the HIV-infected population, data from a total of 19,443 persons (15,414 [79%] men and 4,029 [21%] women) who did not object to further data collection were included in this annual report. Amongst those newly registered in 2011, 61% received the diagnosis of HIV in 2011, whereas 15% had received the diagnosis in 2010.

Of the 15,414 men with HIV, 209 (1%) were younger than 18 years of age at diagnosis, 6,328 (41%) were 18 to 34 years, 7,732 (50%) were 35 to 54 years, and 1,059 (7%) were 55 years or older. Of the 4,029 women with HIV, 244 (6%) were younger than 18 years of age at diagnosis, 2,474 (61%) were 18 to 34 years, 1,132 (28%) were 35 to 54 years, and 158 (4%) were 55 years or older. The date of HIV diagnosis and, therefore, age at diagnosis is still unknown for 86 men and 21 women.

Of the 1,100 men who were registered in 2011, 1% were younger than 18 years of age, 38% were 18 to 34 years, 45% were 35 to 54 years, and 10% were 55 years or older at HIV diagnosis. Of the 237 women registered in 2011, 8% were younger than 18 years of age, 43% were 18 to 34 years, 35% were 35 to 54 years, and 7% were 55 years or older at HIV diagnosis. The date of HIV diagnosis was unknown for 61 (6%) men and 15 (6%) women.

Table 4: Cumulative numbers and percentages of HIV-infected patients registered and monitored by SHM in one of the HIV Treatment Centres in the Netherlands and Curaçao on 31 December 2011

HIV Treatment Centre	Location	Total N	Total %	Alive N	Alive %	Deaths N	Deaths %	AIDS N	AIDS %	In follow-up N	In follow-up %	Lost to follow-up N	Lost to follow-up %	Deaths before 2011 N	Deaths before 2011 %
Adults															
MCA	Alkmaar	261	1.3	240	92.0	21	8.0	72	27.6	209	80.1	32	12.3	20	7.7
Flevo Zkh	Almere	116	0.6	114	98.3	2	1.7	37	31.9	111	95.7	4	3.4	1	0.9
AMC-UvA	Amsterdam	2,576	13.2	2,311	89.7	265	10.3	745	28.9	2,042	79.3	281	10.9	253	9.8
MC Jan van Goyen	Amsterdam	607	3.1	577	95.1	30	4.9	104	17.1	549	90.4	31	5.1	27	4.4
OLVG	Amsterdam	2,827	14.5	2,542	89.9	285	10.1	769	27.2	2,204	78.0	349	12.3	274	9.7
St Lucas Andreas Zkh	Amsterdam	318	1.6	284	89.3	34	10.7	102	32.1	264	83.0	23	7.2	31	9.7
Slotervaart Zkh	Amsterdam	802	4.1	672	83.8	130	16.2	245	30.5	595	74.2	87	10.8	120	15.0
VUMC	Amsterdam	503	2.6	439	87.3	64	12.7	162	32.2	374	74.4	68	13.5	61	12.1
Rijnstate	Arnhem	610	3.1	554	90.8	56	9.2	149	24.4	502	82.3	53	8.7	55	9.0
Haga Zkh - Leyweg	Den Haag	634	3.2	570	89.9	64	10.1	201	31.7	457	72.1	118	18.6	59	9.3
MCH - Westeinde	Den Haag	812	4.2	745	91.7	67	8.3	189	23.3	627	77.2	126	15.5	59	7.3
Catharina Zkh	Eindhoven	478	2.4	454	95.0	24	5.0	83	17.4	389	81.4	67	14.0	22	4.6
MST	Enschede	478	2.4	386	80.8	92	19.2	164	34.3	351	73.4	67	14.0	60	12.6
UMCG	Groningen	730	3.7	672	92.1	58	7.9	202	27.7	608	83.3	65	8.9	57	7.8
Kennemer Gasthuis	Haarlem	375	1.9	334	89.1	41	10.9	96	25.6	300	80.0	36	9.6	39	10.4
MC Leeuwarden	Leeuwarden	237	1.2	215	90.7	22	9.3	55	23.2	189	79.7	28	11.8	20	8.4
LUMC	Leiden	594	3.0	549	92.4	45	7.6	152	25.6	481	81.0	73	12.3	40	6.7
AZM	Maastricht	694	3.6	589	84.9	105	15.1	181	26.1	509	73.3	88	12.7	97	14.0
UMC St Radboud	Nijmegen	586	3.0	526	89.8	60	10.2	165	28.2	489	83.4	41	7.0	56	9.6
Erasmus MC	Rotterdam	2,049	10.5	1,843	89.9	206	10.1	529	25.8	1,623	79.2	241	11.8	185	9.0
Maasstad Zkh	Rotterdam	509	2.6	481	94.5	28	5.5	101	19.8	447	87.8	36	7.1	26	5.1
St Elisabeth Zkh	Tilburg	879	4.5	826	94.0	53	6.0	182	20.7	744	84.6	88	10.0	47	5.3
UMCU	Utrecht	1,377	7.1	1,246	90.5	131	9.5	383	27.8	1,123	81.6	131	9.5	123	8.9
Admiraal de Ruyter Zkh	Vlissingen	129	0.7	118	91.5	11	8.5	33	25.6	97	75.2	21	16.3	11	8.5
Isala Klinieken - Sophia	Zwolle	350	1.8	334	95.4	16	4.6	55	15.7	301	86.0	36	10.3	13	3.7
Total Adults		**19,531**		**17,621**	**90.2**	**1,910**	**9.8**	**5,156**	**26.4**	**15,585**	**79.8**	**2,190**	**11.2**	**1,756**	**9.0**
Children/adolescents															
Emma KZ, AMC-UvA	Amsterdam	67	30.3	67	100	0	0	16	23.9	61	91.0	6	9.0	0	0
Beatrix KK, UMCG	Groningen	18	8.1	18	100	0	0	3	16.7	17	94.4	1	5.6	0	0
Erasmus MC-Sophia	Rotterdam	73	33.0	71	97.3	2	2.7	21	28.8	61	83.6	10	13.7	2	2.7
Wilhelmina KZ, UMCU	Utrecht	63	28.5	62	98.4	1	1.6	13	20.6	53	84.1	9	14.3	1	1.6
Total children/adolescents		**221**		**218**	**98.6**	**3**	**1.4**	**53**	**24.0**	**192**	**86.9**	**26**	**11.8**	**3**	**1.4**
Total Netherlands		**19,752**		**17,839**	**90.3**	**1,913**	**9.7**	**5,209**	**26.4**	**15,777**	**79.9**	**2,216**	**11.2**	**1,759**	**8.9**
Curaçao															
SEHOS	Willemstad	750	97.9	602	80.3	148	19.7	196	26.1	445	59.3	160	21.3	145	19.3
SEHOS kinderkliniek	Willemstad	16	2.1	6	37.5	10	62.5	6	37.5	1	6.3	5	31.3	10	62.5
Totaal Curaçao		**766**		**608**	**79.4**	**158**	**20.6**	**202**	**26.4**	**446**	**58.2**	**165**	**21.5**	**155**	**20.2**

Table 5: New HIV diagnosed patients registered and monitored in 2011 in one of the HIV treatment centres in the Netherlands and Curaçao

HIV Treatment Centre	Location	Total N	Total %	Alive N	Alive %	Deaths N	Deaths %	AIDS N	AIDS %	In follow-up N	In follow-up %	Lost to follow-up N	Lost to follow-up %
Adults													
MCA	Alkmaar	15	1.1	14	93.3	1	6.7	2	13.3	15	100	0	0
Flevo Zkh	Almere	18	1.3	17	94.4	1	5.6	11	61.1	18	100	0	0
AMC-UvA	Amsterdam	91	6.8	91	100	0	0	5	5.5	91	100	0	0
MC Jan van Goyen	Amsterdam	42	3.1	42	100	0	0	1	2.4	42	100	0	0
OLVG	Amsterdam	179	13.4	179	100	0	0	22	12.3	179	100	0	0
St Lucas Andreas Zkh	Amsterdam	30	2.2	29	96.7	1	3.3	2	6.7	30	100	0	0
Slotervaart Zkh	Amsterdam	22	1.6	22	100	0	0	0	0	22	100	0	0
VUMC	Amsterdam	31	2.3	31	100	0	0	4	12.9	31	100	0	0
Rijnstate	Arnhem	43	3.2	42	97.7	1	2.3	4	9.3	43	100	0	0
Haga Zkh – Leyweg	Den Haag	26	1.9	26	100	0	0	3	11.5	26	100	0	0
MCH – Westeinde	Den Haag	72	5.4	68	94.4	4	5.6	8	11.1	72	100	0	0
Catharina Zkh	Eindhoven	42	3.1	42	100	0	0	1	2.4	42	100	0	0
MST	Enschede	93	7.0	63	67.7	30	32.3	47	50.5	65	69.9	0	0
UMCG	Groningen	28	2.1	28	100	0	0	3	10.7	28	100	0	0
Kennemer Gasthuis	Haarlem	24	1.8	24	100	0	0	0	0	24	100	0	0
MC Leeuwarden	Leeuwarden	16	1.2	16	100	0	0	3	18.8	16	100	0	0
LUMC	Leiden	53	4.0	51	96.2	2	3.8	8	15.1	53	100	0	0
AZM	Maastricht	48	3.6	48	100	0	0	7	14.6	48	100	0	0
UMC St Radboud	Nijmegen	33	2.5	33	100	0	0	5	15.2	33	100	0	0
Erasmus MC	Rotterdam	150	11.2	147	98.0	3	2.0	13	8.7	150	100	0	0
Maasstad Zkh	Rotterdam	72	5.4	72	100	0	0	4	5.6	72	100	0	0
St Elisabeth Zkh	Tilburg	81	6.1	81	100	0	0	5	6.2	81	100	0	0
UMCU	Utrecht	80	6.0	80	100	0	0	11	13.8	80	100	0	0
Admiraal de Ruyter Zkh	Vlissingen	19	1.4	19	100	0	0	3	15.8	19	100	0	0
Isala Klinieken – Sophia	Zwolle	29	2.2	29	100	0	0	3	10.3	29	100	0	0
Total Adults		**1,337**	**100**	**1,294**	**96.8**	**43**	**3.2**	**175**	**13.1**	**1,309**	**97.9**	**0**	**0**
Children/adolescents													
Emma KZ, AMC-UvA	Amsterdam	11	39.3	11	100	0	0	2	18.2	11	100	0	0
Beatrix KK, UMCG	Groningen	6	21.4	6	100	0	0	0	0	6	100	0	0
Erasmus MC-Sophia	Rotterdam	7	25.0	7	100	0	0	2	28.6	7	100	0	0
Wilhelmina KZ, UMCU	Utrecht	4	14.3	4	100	0	0	0	0	4	100	0	0
Total children/adolescents		**28**	**100**	**28**	**100**	**0**	**0**	**4**	**14.3**	**28**	**100**	**0**	**0**
Curaçao													
SEHOS	Willemstad	68	100	65	95.6	3	4.4	7	10.3	65	95.6	0	0

Registration of HIV-infected adults

Out of a total of 19,443 people registered through the end of 2011, 13,682 (79%) were adult men and 3,650 (21%) were adult women. Amongst men, homosexual contact was by far the greatest risk factor (72%), whereas heterosexual transmission was the greatest risk factor (89%) amongst women. The median age at diagnosis was 36.6 years (IQR, 30.1-43.9) for men and 30.8 (25.3-37.6) for women. Five percent of the total population had known their HIV status for less than a year, 26% had known for 1 to 5 years, 29% for 5 to 10 years, and 39% for more than 10 years.

Of the 1,263 adults who were registered in 2011 and whose data was processed by the end of 2011, 1,050 (83%) were men, and 213 (17%) were women. Homosexual contact was still the most frequent risk factor amongst men (72%) and heterosexual contact amongst women (88%). The median age at diagnosis was 38.0 years (IQR, 29.7-46.9) in men and 34.4 (27.0-43.6) in women. Of the registered persons, 63% had known their HIV status for less than a year, 20% for 1 to 5 years, 4% for 5 to 10 years, and 5% for more than 10 years. The date of diagnosis was unknown for the remaining 8%.

Registration of HIV-infected children

As of 31 December 2011, 202 children aged 17 years or younger were registered as HIV-positive. Amongst that group, 103 (51%) were boys and 99 (49%) were girls. The median age at diagnosis was 1.5 years (IQR 0.4-4.9) for boys and 2.0 (0.4-4.5) for girls. In 2011, 5 HIV diagnoses were recorded in this age group. Vertical mother-to-child transmission was the route of infection in almost all (89%) of the cases; apart from that, a few cases were recorded as sexually transmitted. In total, 43% of the infected children were of Dutch origin, and 49% originated from sub-Saharan Africa.

Registration of HIV-infected pregnant women

In 2011, the number of registered pregnancies increased to 2,251 in a total of 1,390 HIV-infected women. In 55% of the cases, HIV was diagnosed before the start of the pregnancy, and it was diagnosed in 45% during the pregnancy. The transmission route of HIV amongst the pregnant women was mostly through heterosexual contact (93%); in 2% transmission was through injecting drug use. The median age during the first pregnancy was 29 years (IQR, 24-33). In 33% of the women, cART was started before the onset of the first pregnancy and in 63% during the pregnancy. In 19%, gestation lasted less than 16 weeks; in those who were still pregnant after the initial 16 weeks, the median gestation was 39 weeks (IQR, 37–40).

Monitoring of HIV-infected adults and children

The median follow-up for the population of infected adults was 7.0 years (IQR, 3.2-12.5), with 6.8 years for men and 7.6 years for women. For children, the median follow-up was 7.2 years (IQR, 3.2–10.2). The total follow-up in 2011 in the adult population was 144,926 person years and for children 1,437 person years.

Monitoring of treatment

Most HIV-infected patients in 2011 lived in the western part of the country; 74% of the patients were being monitored in one of the centres in the Randstad, which comprises the large cities of Amsterdam, The Hague, Leiden, Rotterdam, and Utrecht.

In 2011, 85% percent of the registered infected adults were being treated with cART, 14.3% were not being treated, and treatment information was unknown for 1.3% (in most cases, this was because such data were not yet registered).

The median CD4-cell count at the time of HIV diagnosis was 340 cells/mm^3 (IQR, 146-540) for the adult population. This number decreased to 230 cells/mm^3 (IQR, 110-330) at the start of cART. Since 2005, an increase in CD4-cell counts has been seen at the start of cART.

After 24 weeks of treatment, 89% of the patients had an HIV-RNA plasma concentration below 500 copies/ml; after 48 weeks this percentage decreased to 87%. In 94% of the treated population, the most recently measured HIV-RNA plasma concentration was lower than 500 copies/ml.

More than 92% of the initial cART regimens used in 2011 consisted of tenofovir combined with emtricitabine as the nucleotide/nucleoside HIV-1 reverse transcriptase inhibitor (NRTI) backbone. Efavirenz was the most common addition to this backbone, followed by ritonavir-boosted darunavir. In 2011, efavirenz was used in 444 (50%) and darunavir/ritonavir in 144 (16%) of the first-line cART regimens. The integrase inhibitor raltegravir was used in 33 (4%) of the first-line regimens. The most popular initial cART regimen in 2011 was tenofovir+emtricitabine+efavirenz *(Table 6)*, followed by tenofovir+emtricitabine+nevirapine and then tenofovir+emtricitabine+atazanavir/ritonavir.

The AIDS incidence in the cART-treated population has declined since the introduction of cART in 1996 from 14.1 (95% CI, 11.3-17.4) per 100 person-years of follow-up to 1.02 (0.84-1.22) in 2010. The overall mortality rate in the treated group also decreased from 4.7 (95% CI, 3.1-6.7) in 1996 to 0.99 (0.83-1.19) in 2010.

Monitoring of resistance

Data were obtained regarding the results of genotyping of the protease gene and HIV reverse transcriptase from five out of seven virology laboratories involved in the monitoring of resistance. A total of 10,498 sequences were collected *(Table 7)*; 254 of those were collected in 2011.

In 128 (10%) of the 1,283 patients with a recent infection in or after 2002, one or more resistance-associated mutations was found. Similarly, 296 (10%) of the 2,894 patients with a recent diagnosis had at least one mutation. In 2011, of the 69 newly diagnosed patients, 8 (12%) were resistant, whereas 3 (9%) of the 34 recently infected patients were resistant.

Table 6: Most frequently used initial cART combination 2009–2011 (cART=combination antiretroviral therapy, TDF=tenofovir, FTC=emtricitabine, EFV=efavirenz, NVP=nevirapine, ATV/r=atazanavir/ritonavir, DRV/r=darunavir/ritonavir, AZT=zidovudine, 3TC=lamivudine, LOP/r=lopinavir/ritonavir, RAL=raltegravir, ABC=abacavir, SAQ/r=saquinavir/ritonavir, d4T=stavudine)

More than 92% of the initial cART regimens used in 2011 consisted of tenofovir combined with emtricitabine as the nucleotide / nucleoside HIV-1 reverse transcriptase inhibitor backbone. Efavirenz was the most frequently used supplementation to this backbone, followed by ritonavir boosted darunavir. In 2011, efavirenz was used in 444 (50%) and darunavir/ritonavir in 144 (16%). The integrase inhibitor raltegravir was used in 33 (3.8%) initial cART regimens.

	2009		2010		2011		Total	
	N	%	N	%	N	%	N	%
Total number of patients commencing first cART regimen	1,315	100.0	1,334	100.0	877	100.0	3,526	100.0
TDF+FTC+EFV	735	55.9	727	54.5	428	48.8	1890	53.6
TDF+FTC+NVP	135	10.3	136	10.2	82	9.4	353	10.0
TDF+FTC+ATV/r	96	7.3	111	8.3	94	10.7	301	8.5
TDF+FTC+DRV/r	18	1.4	116	8.7	129	14.7	263	7.5
AZT+3TC+LOP/r	57	4.3	45	3.4	28	3.2	130	3.7
TDF+FTC+LOP/r	67	5.1	28	2.1	18	2.1	113	3.2
TDF+FTC+LOP/r+EFV	43	3.3	24	1.8	18	2.1	85	2.4
TDF+FTC+RAL	30	2.3	15	1.1	14	1.6	59	1.7
AZT+3TC+NVP	21	1.6	20	1.5	4	0.5	45	1.3
TDF+FTC+EFV+RAL	4	0.3	15	1.1	9	1.0	28	0.8
ABC+3TC+EFV	14	1.1	8	0.6	4	0.5	26	0.7
AZT+3TC+EFV	9	0.7	7	0.5	2	0.2	18	0.5
AZT+3TC+SAQ/r	9	0.7	5	0.4	4	0.5	18	0.5
ABC+3TC+NVP	6	0.5	9	0.7	2	0.2	17	0.5
ABC+3TC+LOP/r	6	0.5	8	0.6	2	0.2	16	0.5
d4T+3TC+NVP	7	0.5	5	0.4			12	0.3
ABC+3TC+DRV/r			3	0.2	7	0.8	10	0.3
Other	58	4.2	52	3.9	32	3.5	142	4.0

Table 7: Number of HIV-1 RT and protease gene sequences generated by virological laboratory and registered as per 31 December 2011 with SHM. ([a]provisional total; [b]numbers not available at time of print)

	Number of sequences obtained		
Laboratory	**Before 2010**	**In 2010**	**Total**
AMC-UvA, Amsterdam	3,913	127[a]	4,04
UMCU, Utrecht	3,586	0[b]	3,586
LUMC, Leiden	1,189	15	1,204
Erasmus MC, Rotterdam	613	43	656
VUMC, Amsterdam	409	33	442
Slotervaart Zkh, Amsterdam	143	36	179
CLB, Amsterdam	391	0	391
Total	**10,244**	**254**	**10,498**

In total, 254 sequences obtained in 2011 were available for analysis. Of these sequences, 59 (23%) harboured at least one resistance-associated mutation. Of these 59 sequences with resistance, 46 (78%) harboured mutations associated with resistance to NRTIs, 11 (19%) had mutations against protease inhibitors, and 24 (41%) had mutations against non-NRTIs.

Monitoring of HBV and HCV co-infections

Infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) can cause hepatic cirrhosis, hepatic fibrosis, and hepatocellular carcinoma. In combination with HIV, the course of such diseases is probably accelerated. Therefore, HBV and HCV are monitored in the HIV-infected population over time. In 2011, a chronic co-infection with HCV was found in 12% of patients with HIV. A co-infection with HBV was found in 8% of patients, and 1% had a co-infection with both HCV and HBV. Of the patients with HBV co-infection, hepatic fibrosis developed in 13%, and hepatic cirrhosis developed in 7%; hepatocellular carcinoma was found in 1%. For patients co-infected with HCV, the totals were 19% (hepatic fibrosis), 8% (hepatic cirrhosis), and 1% (hepatocellular carcinoma).

Registration and monitoring in Curaçao

The registration and monitoring of HIV-infected persons being followed in the St. Elisabeth Hospital in Willemstad, Curaçao, continued during the past year. Results from the monitoring in the Netherlands Antilles in 2011 will be presented in 2012. In total, 766 patients (750 adults and 16 children) were registered; 68 of those were added in 2011.

Sample collection

Since the start of the ATHENA project in 1996, an estimated total of 363,166 plasma samples from patients in follow-up have been stored in the microbiological laboratories at the HIV treatment centres or in laboratories associated with the centres. This sample collection is exceptionally valuable for clinical epidemiologic research, especially that involving

resistance development over the course of time and that involving the response of subtypes of HIV-1, other than the most common subtype B, to antiviral therapy. Results of such research is meaningful both for the quality of care of individual patients and for public health.

Quality of care

In 2011, SHM further developed the programme focusing on the quality of HIV care, which looked at the influence of the quality of care on the outcome of HIV treatment and disease progression. An area of focus in this programme is the timely start of therapy in patients who enter into care at an HIV treatment centre in an early stage of infection. In 2009 and 2010, 6% of patients who entered care with more than 350 CD4 cells/mm^3 were started on therapy with less than 200 CD4 cells/mm^3. The frequency of monitoring HIV patients between entry into care and start of treatment is closely related to the rate of CD4 decline and is important in preventing a late start of treatment. Even after the start of treatment, monitoring of patients plays an important role in the early recognition of treatment failure; with such recognition, the therapy combination can be changed well before the patient is exposed to high HIV viral levels. Through the quality of care programme, SHM will help to determine the optimal frequency for monitoring patients.

Amsterdam Cohort Studies

The Amsterdam Cohort Studies (ACS) on HIV and AIDS were started amongst homosexual men (HM) in 1984 and amongst drug users (DU) in 1985. The ACS were started with the purpose of making epidemiologic, pathogenic, and clinical research on HIV and AIDS possible, thereby contributing to the worldwide fight against HIV/AIDS. The realisation of these studies has been a collaboration involving the Sanquin Blood Supply Foundation, the Municipal Health Service of Amsterdam, the Academic Medical Centre of the University of Amsterdam, and the University Medical Center Utrecht. The ACS is financed through combined contributions of the participating institutes and the National Institute for Public Health and the Environment (RIVM).

The ACS is unique because it allows for follow-up of two populations at risk for HIV infection, that is, the HIV-negative populations of homosexual men and drug users. Those populations are followed by the Municipal Health Service, whereas HIV-infected persons in the ACS are still followed mostly through HIV care and through the monitoring of HIV by SHM. In addition to the provision of care, research material has been provided by patients and stored for specific immunologic and virologic studies. This includes material from persons who were initially HIV-negative and were infected during follow-up, as well as those who began participating in the ACS after being infected subsequent to the study design in 1984-5.

As of 31 December 2010*, 2447 HM and 1657 injecting DU were included in the ACS.
In total, the Public Health Service (PHSA) of Amsterdam was visited 49,647 times by HM and 26,164 times by DU since the start of the ACS. In 2010, 542 HM were followed at the PHSA of Amsterdam. Thirty-six of them had been newly recruited since January 2010, and one participant died. Of the 351 DU that were followed at the PHSA in 2010, 5 had their first study visit in 2010. The HIV-incidence in 2010 was almost 2 per 100 person-years among HM and less than 1 per 100 person-years among DU.

** Note: Total numbers for 2011 were still being collected and were not yet complete at time of print.*

Registration programme

Earlier diagnosis, earlier start of treatment

Of the patients registered by SHM with an HIV-1 infection and a known date of diagnosis as of mid-2011, 79% started cART between January 1995 and December 2010 and had follow-up available after therapy initiation. In recent years, diagnosis and antiretroviral treatment of HIV has entered a new phase reflected in several trends. With time, patients with HIV are being diagnosed at an earlier stage of infection with higher CD4-cell counts, indicating a less impaired immune system. Half of the population in 1996 had CD4-cell counts of 250 cells/mm^3 or higher at the time of diagnosis, whereas half the population in 2010 had 350 cells/mm^3 or higher.

Patients are starting combination antiretroviral therapy (cART) earlier, as is confirmed by the increase in median CD4-cell numbers amongst the patients who started cART between January 1995 and December 2010. Half of the patients who started cART between 1995 and 2005 had CD4 counts of 200 cells/mm^3 or higher. Thereafter, median counts at the start of cART rose to 240 cells/mm^3 between 2005 and 2009 and then to 300 cells/mm^3 in 2010 and 2011.

High levels of HIV suppression

Suppression of HIV production occurred in 58% of patients within 6 months after commencing therapy, for 72% within 9 months and for 80% within 12 months. Over calendar time, suppression of HIV to below 50 copies/ml after 9 months of cART was achieved in 68% of patients starting between 1999 and 2001; it increased to 74% for those starting between 2002 and 2004, to 75% for those starting between 2005 and 2007, and to 83% for those starting between 2008 and 2010.

Sustained suppression measured from 36 weeks of cART up to a maximum of nine years was achieved for 82% to 84%. In cases of uninterrupted cART, figures rose to between 88% and 90%. Nearly normal CD4-cell counts were reached after virologically successful cART, depending on counts at the start of cART.

Declining HIV-related disease and death

HIV-related illness and AIDS have become less frequent, and HIV/AIDS-related death has fallen significantly. The overall mortality rate in the registered population is 12.9 (95% CI, 12.3-13.5) per 1000 person-years, and it has declined over time to 8.9 (95% CI, 7.3-10.6) in 2010. The incidence of AIDS has decreased sharply to between 10 and 20 cases per 1000 patients per year in recent years, although the incidence in 2010 will be approximately 10% higher, when we take the backlog in the registration of AIDS into account.

The mortality rate after the start of cART substantially decreased over calendar time to 9.8 (95% CI, 8.1-11.8) per 1000 person-years in 2010. Also, the incidence of AIDS decreased dramatically to 8.9 per 1000 person-years in 2010.

Despite its decline, the mortality rate is still well above that which would be expected in the same group of individuals if they were not infected with HIV. The excess mortality rate can be explained in part by patients who already had AIDS at the time of their HIV diagnosis. In addition, it may be due to the effects of HIV infection and the use of cART, as well as to factors related to family and lifestyle. However, a subgroup of recently diagnosed, effectively treated patients had a life expectancy similar to the HIV-negative population of the Netherlands. This suggests that effective cART strategies may enable HIV-positive patients to achieve low levels of mortality similar to those in the general population.

Changing causes of death

Causes of death in the HIV-infected population are changing. Amongst patients who died before the start of cART, AIDS is the most common cause of death. Causes of death registered after the start of cART are AIDS in 34% of cases, non-AIDS-defining malignancy in 14%, cardiovascular diseases in 7%, non-natural causes in 5% and other or unknown causes in 40%. Hence, approximately two-thirds of people who were HIV-1-positive and died after starting cART did not die of AIDS, but of other causes. Of the patients who died in 2010, 12 (11%) died of AIDS, 24 (21%) of a non-AIDS-defining malignancy, 8 (7%) of a non-AIDS-defining infection, 5 (4%) of liver failure, 3 (3%) of pulmonary-related causes, 3 (3%) non-natural death, 2 (2%) of cardiovascular disease, 2 (2%) of substance abuse and 64 (56%) of other, unknown or unclassifiable causes.

The median last known CD4 counts are low for all groups of patients, but particularly for those who died of AIDS-defining causes. This implies that HIV infection may play a role in mortality, even if AIDS is not the immediate cause of death. It confirms findings by the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, in which death due to liver disease, non-AIDS malignancies, cardiovascular disease and other non-AIDS-related causes were all associated with lower last known CD4-cell counts, albeit less strongly than death due to AIDS.

Declining AIDS, increasing non-AIDS disease

The overall incidence of first AIDS-defining events after the start of cART is 24.0 (95% CI, 23.0–25.0) per 1000 person-years of follow-up. This incidence fell significantly from 175.4 in 1996 to 14.2 in 2010 ($p<0.0001$), declining rapidly between 1996 and 1998 and more slowly between 1998 and 2011.

The overall incidence of serious non-AIDS-defining diseases after the start of cART is 23.5 (95% CI, 23.5–25.9) per 1000 person-years of follow-up. It rose significantly from 21.1 in 2002 to 29.9 in 2010. A heightened incidence of serious non-AIDS-defining diseases is associated with patients being older, being antiretroviral-therapy experienced at the start of cART, having a lower CD4 count, being positive for hepatitis B or C virus, having a longer time between HIV-1 diagnosis and the start of cART and being either less than a year or more than 11 years in follow-up.

The incidence of renal disease, osteoporosis and non-AIDS malignancy rose over calendar time between the start of monitoring and 2010. The incidence, however, of liver disease, diabetes mellitus, myocardial infarction and stroke did not rise. All serious non-AIDS-related diseases are associated with older age. Independently, low CD4-cell counts are associated with renal disease, liver disease, diabetes mellitus, stroke and non-AIDS-related malignancy, but not with myocardial infarction and osteoporosis. A positive test for HBV or HCV is independently associated with liver disease, as is a longer time of exposure to HIV before starting cART. Gender is associated with only myocardial infarction (males) and osteoporosis (females).

According to age and gender, the incidence of diabetes mellitus, myocardial infarction, osteoporosis and stroke in patients on cART is higher than in the general population of the Netherlands. This is also true for non-AIDS-related malignancies, although the higher incidence with these cancers is restricted to the male HIV-infected population on cART. SHM has begun research to further detail the possible association with HIV-infection itself, the use of cART and patient immune status, as well as differences in lifestyle factors reported in association with these diseases.

In a study of the possible direct effect of HIV on non-AIDS-related diseases, we found that the cumulative number of years spent with periods of HIV RNA levels of 1000 copies/ml or higher was associated only with non-AIDS-related mortality, independent of latest CD4-cell counts. However, this effect disappeared when viral load measurements taken less than six months prior to the end of follow-up were excluded from the calculation of exposure time, indicating that the effect of exposure time to HIV RNA levels of 1000 copies/ml or higher may be partly driven by patients stopping antiretroviral medication during end-stage disease.

HBV/HCV co-infections

Chronic hepatitis B (HBV) and hepatitis C (HCV) infections are associated with progression to chronic liver disease. Amongst the HIV-infected individuals screened for viral hepatitis, the prevalence is 8% for HBV and 12% for HCV co-infection. The majority of co-infected patients were homosexual men, and amongst them, the number of new HCV diagnoses has significantly increased over time. Homosexual men are currently the largest group of individuals co-infected with HCV.

Fifty-nine percent of patients with HIV/HBV and 27% of patients with HIV/HCV received treatment for the co-infection. Anti-HBV treatment is available as part of anti-HIV treatment, and 48% to 65% of the co-infected patients showed a reduction of HBV DNA. Patients with HCV were treated with peginterferon in combination with ribavirin, resulting in an overall sustained virologic response in 45%. Compared to HIV mono-infected patients, the risk of death was not increased amongst those with co-infection. However, both HBV and HCV co-infection were strongly associated with progression to severe chronic liver disease.

Treatment of HBV and especially HCV co-infections is not yet optimal, although direct-acting antiviral drugs exist for HBV and have recently become available for HCV. Hence, prevention of progression to severe chronic liver disease may become feasible, and monitoring of chronic HBV and HCV infection is currently performed by SHM for the HIV co-infected population.

Limited virological failure and resistance

Although a high percentage of patients on cART currently achieve sustained suppression of HIV viral load, a small group achieve only incomplete suppression, which may be a marker of inadequate adherence to therapy and may herald the presence of drug resistance. Incomplete suppression, or virologic failure, is observed in 5% of the treated patients annually.

In approximately 50% to 80% of patients experiencing virologic failure, resistance to the nucleoside reverse transcriptase inhibitors (NRTI's) lamivudine and emtricitabine and to non-NRTI's has been found. Resistance to other NRTI's and protease inhibitors has been found only in a substantial proportion of patients previously treated with non-cART regimens. Altogether, 10% of patients currently in follow-up are resistant to at least one antiretroviral drug. This proportion is an underestimation, since results of genotypic resistance measurements are obtained in less than one third of patients with virologic failure.

Evidence of transmission of resistant virus is found in less than 5% of patients, indicating that infections from the reservoir of treated patients with resistance are relatively rare and that new infections occur mainly via untreated HIV-infected individuals who may not yet be aware of their infection.

cART and the HIV epidemic

Since the 1990s, the annual number of diagnoses amongst MSM steadily increased to just above 800 in 2008. The registered number of diagnoses in 2009 and 2010 was, however, considerably lower than in 2008. In part, this lower number is the result of a backlog in the registration of HIV cases due to the visit-based data collection by SHM. However, even when this backlog is taken into account, the expected number of diagnoses in these years would be approximately only 750, which is lower than in 2008, but comparable to that in 2007.

In the heterosexual population, the annual number of diagnoses reached a maximum around 2004 and then has declined to approximately 300 cases annually in recent years. When a backlog in registration was considered, the number of diagnoses appeared not to decrease any further in 2009 and 2010.

Injecting drug use is rarely reported any longer as the most probable mode of transmission, which reflects the decreasing popularity of injecting drugs since the 1980s. Also, needle exchange programmes and easily accessible dispensing of methadone has contributed greatly to a reduction in the number of new infections in this group.

Hence, evidence is accumulating that the increasing trend in the number of new diagnoses amongst men who have sex with men (MSM) has halted. Alternatively, 2007 and 2008 may be years with an excess of new diagnoses, which caused a rise above the long-term trend because of the introduction of opt-out testing for HIV at major sexually transmitted infection (STI) clinics at about that time. It is of interest that the proportion of recent infections amongst the new diagnoses has increased.

The increase in CD4 counts at diagnosis and the ensuing decrease in proportion of late diagnoses suggests that patients are testing positive for HIV increasingly earlier in the course of their infection. This earlier diagnosis is also apparent in the observed increase from 10% in 1996 to 39% in 2011 in the proportion of MSM who were diagnosed with a recent infection. Diagnosis with a recent infection was more common in younger MSM. Also, the proportion of recent infections amongst heterosexuals appeared to increase from 5% in 1996 to 10% in 2011.

Since the proportion of recent infections, as well as CD4 counts at diagnosis, has increased amongst those diagnosed with HIV, testing for HIV has apparently become more common.

Decreasing late presenters and start of treatment

Overall, 55% of the patients were late presenters, i.e., individuals either presenting for care with a CD4-cell count below 350 cells/mm^3 or presenting with an AIDS-defining event regardless of the CD4 count. In recent years, between 10% and 15% of the patients already had AIDS at the time of diagnosis.

Although the proportion of late presenters has decreased over time, in 2011 38% of MSM, 64% of heterosexual men, and 51% of heterosexual women were still diagnosed late in the course of their infection. Similar patterns were observed in the proportion of patients presenting for care with advanced HIV disease.

Amongst heterosexuals who had an HIV diagnosis in 2008 or later, patients of sub-Saharan African origin more often presented with a late-stage infection (73%) compared to those of Dutch origin (56%). Late presentation was also more common in patients diagnosed at older ages.

Late presentation was in part responsible for the late start of treatment. In patients who were diagnosed in 2009 or later with CD4 counts below 350 cells/mm^3 and who were thus eligible for treatment, there was almost no delay between their HIV diagnosis and start of treatment. Within three months of their HIV diagnosis, 75% of these patients had started treatment, and after one year, 93% had done so. For those who had more than 350 CD4-cells/mm^3 at diagnosis, CD4 counts at the start of treatment were 370 (IQR, 310-480) cells/mm^3, with 62% of the patients starting in time.

In recent years, cART has been started increasingly earlier in the course of HIV infection as evidenced by higher CD4 counts at the start of treatment since the mid-2000s. In 2010, median CD4 counts at the start of treatment were 290 (IQR, 173-360) cells/mm^3. Hence, more than 25% of the HIV-infected patients started treatment according to the current guidelines, which recommend starting before CD4 counts cross the threshold of 350 cells/mm^3. However, a large group of patients still began treatment with CD4 counts below 200 cells/ mm^3, which is considered a late start.

Current first-line cART combinations

In 2010 and 2011, 73% of all first-line cART regimens for therapy-naive patients included a combination of tenofovir/emtricitabine and efavirenz, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir. This is in accordance with the current guidelines. An additional 10% of the regimens were a combination of tenofovir/emtricitabine and nevirapine; 17% of the patients started other, most likely individual-based, combinations.

Dutch guidelines do not recommend raltegravir as part of the first-line regimen, because potential long-term side-effects of raltegravir have been unexplored. More importantly, raltegravir is a twice-daily drug, whereas national guidelines favour once-daily regimens. Consequently, only 1% of those starting cART, or 14 patients in total, started this combination.

Conclusion & Recommendations

The health and life expectancy of individuals infected with HIV have improved substantially. That is largely the result of highly effective cART, which enables improved levels of suppression of HIV production for a prolonged period of time.

Improved testing policies now give people at risk the opportunity to be regularly checked for HIV, and an increasing number are being tested. Consequently, when testing is positive, people are still in an early phase of infection and can be treated earlier. This year's report shows the continuing increase in the number of infected individuals who start treatment early.

People with HIV who are treated early on have an improved long-term immune response to cART, reaching higher and more often nearly normal CD4-cell counts.

Current guidelines for the start of cART have resulted in a high level of evidence-based standardised combinations of first-line antiretroviral drugs. Once therapy is begun, individuals remain on their first-line regimen for a longer time, which indicates fewer side effects and less drug toxicity. It also points to the regular and well managed follow-up of patients on therapy. A relatively low annual percentage (5%) of the individuals on cART experience virologic failure. A high percentage of these, however, have HIV resistant to one or more of the drugs used but because the total group is limited, transmission of resistant HIV is also limited. However, figures are less reliable since systematic resistance measurement is in urgent need of improvement.

By the end of 2011, 19,752 patients were registered in the Netherlands, with a total follow-up time since diagnosis of 161,481 person-years. Compared to last year, the registered population has increased by 1372 patients, or 7%. The majority were diagnosed with HIV in 2010 and 2011, but 24% were diagnosed in or prior to 2009.

From 2009 to 2011, the increase in the annual number of new HIV diagnoses amongst MSM stabilised to an estimated 750. This is a promising result, as it may reflect an improved awareness of the risk of infection and the need for regular HIV testing.

Despite these impressive figures showing the importance of large-scale anti-HIV treatment in combination with effective HIV testing strategies, AIDS is still an important cause of death amongst HIV-infected individuals. Too many infected individuals are tested late, with a late start of cART. In addition, the mortality rate is still higher amongst HIV-infected individuals than amongst those who are not infected.

Large-scale treatment also has changed the morbidity and causes of death in the HIV-infected population. Serious non-AIDS-related diseases occurring after the start of cART include renal disease, osteoporosis and non-AIDS-related malignancy, and incidences have risen since the introduction of cART. Liver disease, diabetes mellitus, myocardial infarction and stroke are diagnosed in the HIV-infected population, as well. All non-AIDS-related diseases are associated with older age, indicating that cART has increased the life expectancy of HIV-infected people.

However, the incidence of diabetes mellitus, myocardial infarction, osteoporosis and stroke is higher in the HIV-infected cART-treated population than in the general population of the Netherlands, as is true for males with non-AIDS-related malignancies. A direct effect of HIV or effects of long-term cART may play a role, and further research will be carried out as part of the HIV aging project.

Liver disease is associated with chronic HBV or HCV infections, which are prevalent in the HIV-infected population. Antiviral treatment of HBV and HCV is expected to substantially change the pattern of liver-related disease. However, follow-up of patients treated with anti-HBV drugs is still relatively short, and antiviral treatment of HCV has started only very recently. Data management and data collection are currently being adapted to enable proper follow-up of HBV and HCV.

Large-scale cART, because of its HIV suppressive efficacy, may help contain the spread of HIV, especially when adherence is high and it is combined with an HIV testing policy that aims at finding infected individuals early in the course of disease and providing early treatment. In that way, the window of opportunity of transmission is diminished, and together with other means of primary prevention, it is probably the only way until a protective vaccine is available.

However, since cART does not eradicate HIV from the body, large-scale adoption of an early start of lifelong cART is not without risks. HIV resistance will inevitably grow, albeit perhaps slowly, along with transmission of resistant HIV. Together with uncertainties regarding adherence to lifelong cART and its toxicity and the role of cART and HIV in the early aging process of those infected, such a large-scale adoption of early cART stresses the need for continuing high quality standards of HIV care and monitoring.

Collaborations

National collaborations

AMC-UvA

SHM collaborates with the Academic Medical Center (AMC) of the University of Amsterdam (UvA) on various projects. The Co-morbidity and Aging with HIV study, led by Prof. Peter Reiss (Department of Internal Medicine, AMC, Amsterdam) and supported by a grant from Zon-Mw, aims to assess the incidence and prevalence of a broad range of co-morbidities and known risk factors for these co-morbidities in HIV-infected patients. SHM collaborates with the AMC in this study by providing the data collection infrastructure for monitoring the incidence and prevalence of a number of these co-morbidities. The results obtained from this research may be used to inform and adapt national and international guidelines for prevention and management of co-morbidities in aging HIV-infected individuals.

In a separate project, the AMC and SHM collaborate with Imperial College, London and the British Sanger Institute on a study of viral whole-genome association. The aim of this study is to identify viral virulence factors, which could ultimately shed new light on the pathogenesis of the HIV-1 virus.

CIb-RIVM

The Centre of Disease Control (CIb, headed by Prof. Roel A. Coutinho) of the National Institute for Public Health and the Environment (RIVM), receives and coordinates data on the registration of new HIV infections within the framework of the national HIV registration and surveillance programme.

The registration activities of SHM are associated with the CIb in regard to HIV and other sexually transmitted diseases such as hepatitis B (HBV) and hepatitis C (HCV), as well as infectious diseases such as tuberculosis. The CIb-RIVM and SHM agreed at the beginning of 2009 to exchange data collected through the SHM framework for surveillance purposes carried out by the CIb-RIVM.

As of 1 January 2012, SHM's funding from the Ministry of Health, Welfare and Sport will be routed via the RIVM.

GGD Amsterdam

SHM collaborates with the Public Health Service of Amsterdam (GGD Amsterdam) researching the changes in transmission of HIV since the introduction of HAART, introduction of subtypes other than HIV-1 subtype B in the Netherlands and transmission of HIV strains that are resistant to antiviral agents. SHM and GGD Amsterdam also work together on the Amsterdam Cohort Studies (ACS, reviewed earlier in the report), in collaboration with the AMC-UvA.

NVHB

The Dutch Association of HIV-treating Physicians (NVHB) and SHM collaborated in 2011 on a report examining the Quality of HIV Care in the Netherlands. The aim of this report was to evaluate the overall quality of HIV care in the Netherlands, especially at the treatment centre level. The final report was published in April 2011, with the findings that the overall standard of HIV care in the Netherlands is good and there are no significant differences in the quality of HIV care provided by individual treatment centres compared to the national average.

Visible Care (ZiZo)

The Visible Care (Zichtbare Zorg, ZiZo) programme is run by the Public Health Inspection Agency and is commissioned by the Ministry of Health, Welfare and Sport to allow comparison of health care quality within the health care sector. In 2010 and 2011, SHM was a member of the HIV working group of Zichtbare Zorg and contributed to the development of quality indicators providing insight into HIV care. SHM also carried out a pilot study to test these quality indicators and then assisted in rolling out these quality indicators to all HIV treatment centres.

International collaborations

DIDE

The Department of Infectious Disease Epidemiology (DIDE) is part of the Faculty of Medicine, Imperial College in London. Prof. Sir Roy Anderson, Prof. Geoffrey Garnett, Prof. Christophe Fraser, and Dr. Tim Hallett coordinate the collaboration with SHM. DIDE and SHM have collaborated since 2002, focusing on DIDE's statistical and mathematical support of SHM for analysis of observational cohort data and execution of the HIV registration programme. An important goal of the DIDE research programme is to gain more insight into the interplay of variables that determine the typical progress of infection in a host or in a particular population. Techniques that can provide answers to such questions include the study of the qualities of nonlinear differential equations, organisation and management of large-scale field studies into the transmission and control of an infection in populations, and analysis of large data sets.

The long-standing collaboration with DIDE has resulted in a model analysing the impact of large-scale administration of cART on the epidemic in the Netherlands and in another model comparing quality of care in the Netherlands. Yet another study focuses on the variation in HIV-1 plasma RNA set-points, the clustering around those set-points that maximise the transmission potential and the changes in viral set-point over time.

In a separate project, the DIDE and SHM collaborate with the AMC-UvA and the Sanger Institute, UK, on a viral whole-genome association study. The aim of this study is to identify

viral virulence factors, which could ultimately shed new light on the pathogenesis of the HIV-1 virus.

Frank de Wolf, Director of SHM, is Professor of Clinical Retrovirology at Imperial College, London.

ACHI$_E$V$_{2E}$

ACHI$_E$V$_{2E}$ (A Collaboration on HIV-2 Infection) was established in 2005 as a collaboration of 13 observational cohort studies in 10 European countries, Gambia, and North America that record demographic and clinical data on HIV-2-infected patients. Since HIV-2 is mainly found in Western Africa and only occasionally in Western countries, a limited number of studies have specifically focused on HIV-2. In particular, the effect of antiretroviral treatment on outcome has not been studied in detail. The ACHI$_E$V$_{2E}$ collaboration aims to fill this gap in knowledge by studying different aspects of treated HIV-2 infection.

Papers published by ACHI$_E$V$_{2E}$ in 2011 include:

- *Immunovirological Response to Triple Nucleotide Reverse-Transcriptase Inhibitors and Ritonavir-Boosted Protease Inhibitors in Treatment-Naive HIV-2-Infected Patients: The ACHI$_E$V$_{2E}$ Collaboration Study Group.* Benard A, van Sighem A, Taieb A, Valadas E, Ruelle J, Soriano V, Calmy A, Balotta C, Damond F, Brun-Vezinet F, Chene G, Matheron S. *Clin Infect Dis. 2011 May;52(10):1257-1266.*
- *An international collaboration to standardize HIV-2 viral load assays: Results from the 2009 ACHI$_E$V$_{2E}$ quality control study.* Damond F, Benard A, Balotta C, Böni J, Cotten M, Duque V, Ferns B, Garson J, Gomes P, Gonçalves F, Gottlieb G, Kupfer B, Ruelle J, Rodes B, Soriano V, Wainberg M, Taieb A, Matheron S, Chene G, Brun-Vezinet F; for the ACHI$_E$V$_{2E}$ Study Group. *J Clin Microbiol. 2011 Aug 3. [Epub ahead of print]*

ART-CC

The Antiretroviral Therapy Cohort Collaboration (ART-CC) (coordinated by Prof. Jonathan Sterne, University of Bristol) is a long-standing international collaboration, including 19 cohort studies in Europe and North America. ART-CC was initiated to carry out prognostic studies to assess the effect of cART in therapy-naive patients. Prof. Frank de Wolf and Prof. Peter Reiss (Department of Internal Medicine, AMC, Amsterdam) are the principal investigators for this collaboration on behalf of SHM. In 2011, Frank de Wolf was chair of ART-CC's Executive Committee and a member of the Steering Committee. ART-CC has financial support from the Medical Research Council of the United Kingdom.

In 2011, the following articles were published for ART-CC:

- *The effect of injecting drug use history on disease progression and death among HIV-positive individuals initiating combination antiretroviral therapy: collaborative cohort analysis.* Murray M, Hogg R, Lima V, May M, Moore D, Abgrall S, Bruyand M, D'Arminio Monforte A, Tural C, Gill M, Harris R, Reiss P, Justice A, Kirk O, Saag M, Smith C, Weber R, Rockstroh J, Khaykin P, Sterne J; for the Antiretroviral Therapy Cohort Collaboration (ART-CC). *HIV Med. 2011 Aug 7. [Epub ahead of print]*

- *Comparative Effectiveness of Initial Antiretroviral Therapy Regimens: ACTG 5095 and 5142 Clinical Trials Relative to ART-CC Cohort Study.* Mugavero MJ, May M, Ribaudo HJ, Gulick RM, Riddler SA, Haubrich R, Napravnik S, Abgrall S, Phillips A, Harris R, Gill MJ, de Wolf F, Hogg R, Günthard HF, Chêne G, D'arminio Monforte A, Guest JL, Smith C, Murillas J, Berenguer J, Wyen C, Domingo P, Kitahata MM, Sterne JA, Saag MS; on behalf of the AIDS Clinical Trial Group DACS 241 team AIDS Clinical Trial Group Study 5095 team AIDS Clinical Trial Group Study 5142 team and the Antiretroviral Cohort Collaboration (ART-CC). *J Acquir Immune Defic Syndr. 2011 Aug 18. [Epub ahead of print]*

COHERE

The Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) is a unique collaboration of cohorts in Europe that helps to answer scientific questions requiring a large sample size of patients that the contributing cohorts cannot answer individually and that do not overlap with existing collaborations between participating COHERE cohorts. COHERE'S mission is conduct epidemiological research on the prognosis and outcome of HIV-infected populations from across Europe, including pregnant mothers, children, and adults. Two Regional Coordinating Centres have been established, one in Bordeaux and one in Copenhagen.

Twelve papers have been published to date. In 2011, publications included:

- *Risk of triple-class virological failure in children with HIV: a retrospective cohort study*. Pursuing Later Treatment Options II (PLATO II) project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE), Castro H, Judd A, Gibb DM, Butler K, Lodwick RK, van Sighem A, Ramos JT, Warsawski J, Thorne C, Noguera-Julian A, Obel N, Costagliola D, Tookey PA, Colin C, Kjaer J, Grarup J, Chene G, Phillips A. *Lancet. 2011 May 7;377(9777):1580-7.*
- *HIV-1-related Hodgkin lymphoma in the era of combination antiretroviral therapy: incidence and evolution of CD4+ T-cell lymphocytes*. Bohlius J, Schmidlin K, Boué F, Fätkenheuer G, May M, Caro-Murillo AM, Mocroft A, Bonnet F, Clifford G, Paparizos V, Miro JM, Obel N, Prins M, Chêne G, Egger M; Collaboration of Observational HIV Epidemiological Research Europe (COHERE). *Blood. 2011 Jun 9;117(23):6100-8.*
- *Trends in virological and clinical outcomes in individuals with HIV-1 infection and virological failure of drugs from three antiretroviral drug classes: a cohort study.* The Pursuing Later Treatment Option II (PLATO II) project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Group. *Lancet Infect Dis. 2011 Oct 7. [Epub ahead of print]*
- *All-cause mortality in treated HIV-infected adults with CD4 ≥500/mm³ compared to the general population: evidence from a large European observational cohort collaboration.* The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. *Int. J. Epidemiol. Advance Access published November 28, 2011; doi: 0.1093/ije/dyr164.*
- *Calendar time trends in the incidence and prevalence of triple-class virologic failure in antiretroviral drug experienced people with HIV in Europe.* Nakagawa F for the PLATO II group for COHERE in EuroCoord. *JAIDS 2011 Nov 11. [Epub ahead of print]*

D:A:D Study

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) is a prospective multi-cohort study that focuses on the early recognition of adverse events, amongst which are cardiovascular problems and liver and renal diseases that could result from HIV treatment with antiretroviral agents. Jens Lundgren (Department of Infectious Diseases, Hvidovre Hospital, Copenhagen) coordinates the study, and Prof. Peter Reiss (Department of Internal Medicine, AMC, Amsterdam) is the principal investigator for SHM/ATHENA.

Publications related to the D:A:D study in 2011 include:

- *Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study*. Petoumenos K, Worm S, Reiss P, de Wit S, d'Arminio Monforte A, Sabin C, Friis-MÃ¸ller N, Weber R, Mercie P, Pradier C, El-Sadr W, Kirk O, Lundgren J, Law M; for the D:A:D Study Group. *HIV Med. 2011 Aug;12(7):412-421. Epub 2011 Jan 20.*
- *Elevated triglycerides and risk of MI in HIV-positive persons, the D:A:D study*. Worm SW, Kamara DA, Reiss P, Kirk O, El-Sadr W, Fux C, Fontas E, Phillips A, Monforte AD, De Wit S, Petoumenos K, Friis-Moller N, Mercie P, Lundgren J, Sabin C. *AIDS. 2011 May 30. [Epub ahead of print]*
- *The Coding Causes of Death in HIV (CoDe) Project: Initial Results and Evaluation of Methodology*. Kowalska JD, Friis-Møller N, Kirk O, Bannister W, Mocroft A, Sabin C, Reiss P, Gill J, Lewden C, Phillips A, D'arminio Monforte A, Law M, Sterne J, De Wit S, Lundgren JD; for The CoDe Working Group and the D:A:D Study Group. *Epidemiology. 2011 Jul;22(4):516-523.*
- *The impact of fasting on the interpretation of triglyceride levels for predicting myocardial infarction risk in HIV-positive individuals: The D:A:D Study*. Kamara DA, Worm SW, Reiss P, Rickenbach M, Phillips A, Kirk O, Monforte AD, Bruyand M, Law M, De Wit S, Smith C, Pradier C, Lundgren JD, Sabin C. J *Infect Dis. 2011 Aug;204(4):521-525*.

ECDC

The European Centre for Disease Prevention and Control (ECDC) is an EU agency that aims to strengthen Europe's defences against infectious diseases. ECDC works in partnership with national health protection bodies across Europe to improve and develop continent-wide disease surveillance and early warning systems. By working with experts throughout Europe, ECDC pools Europe's health knowledge to develop authoritative scientific opinions about the risks posed by current and emerging infectious diseases.

In 2011, SHM continued its leading role in a collaborative project to better estimate the prevalence of HIV in Europe and within individual European countries. This project was commissioned by the European Centre for Disease Control and Prevention (ECDC) in Stockholm. SHM collaborates in this project together with Prof. Geoff Garnett from the Department of Infectious Disease Epidemiology (DIDE) at Imperial College in London, Prof. Andrew Phillips from the Department of Population Health at University College London and Prof. Matthias Egger from the Institute of Social and Preventive Medicine at the University of Bern.

EuroCoord

The European Coordinating Committee for the Integration of Ongoing Coordination Actions Related to Clinical and Epidemiological HIV Research (EuroCoord) was established by several of the largest HIV cohorts and collaborations within Europe - CASCADE, COHERE, EuroSIDA and PENTA. The overall aim of EuroCoord is to use the scientific strengths of each collaboration to ensure that the best, most competitive research is performed. It is a large, integrated network with a common virtual database, which currently contains data from over 250,000 HIV-infected individuals from many different settings within and outside Europe. EuroCoord's multidisciplinary approach allows HIV research into a number of key areas aimed at improving the management and life of HIV-infected individuals, whilst also allowing exploration into differences within sub-groups.

In 2011, Prof. Frank de Wolf was chair of EuroCoord's governing body, the Council of Partners.

SHM also participates in the EuroCoord CHAIN (Collaborative HIV and Anti-HIV Drug Resistance Network) project. CHAIN is a large-scale integrated project designed to effectively and durably combat new and existing anti-HIV drug resistance in clinical settings, with a special emphasis on Eastern Europe and in heavily affected resource-poor regions in Africa. The objective is to compare virological, immunological and clinical outcome up to 12-16 months after initiation of cART, according to markers of virus variability (specific mutations, subtypes), with relevance to the drugs in the regimen.

Papers published for EuroCoord in 2011 include:

- *Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study.* Wittkop L, Günthard HF, de Wolf F, Dunn D, Cozzi-Lepri A, de Luca A, Kücherer C, Obel N, von Wyl V, Masquelier B, Stephan C, Torti C, Antinori A, García F, Judd A, Porter K, Thiébaut R, Castro H, van Sighem AI, Colin C, Kjaer J, Lundgren JD, Paredes R, Pozniak A, Clotet B, Phillips A, Pillay D, Chêne G; for the EuroCoord-CHAIN study group. *Lancet Infect Dis. 2011 May;11(5):363-371. Epub 2011 Feb 25.*
- *Insufficient antiretroviral therapy in pregnancy: missed opportunities for prevention of mother-to-child transmission of HIV in Europe.* European Collaborative Study in EuroCoord. *Antivir Ther. 2011;16(6):895-903.*
- *Early antiretroviral therapy in HIV-1-infected infants, 1996-2008: treatment response and duration of first-line regimens.* Judd A; European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group in EuroCoord. *AIDS. 2011 Nov 28;25(18):2279-87.*
- *Prevention of mother-to-child transmission of human immunodeficiency virus among pregnant women using injecting drugs in Ukraine, 2000-10.* Thorne C, Semenenko I, Malyuta R; Ukraine European Collaborative Study Group in EuroCoord. *Addiction. 2012 Jan;107(1):118-28. Epub 2011 Oct 12.*

EuroSIDA

The EuroSIDA study is a prospective observational cohort study of more than 16,500 patients followed in 103 hospitals in 32 European countries plus Israel and Argentina. The main objective of the study is to assess the impact of antiretroviral drugs on the outcome of the general population of HIV-infected patients living in Europe. The primary hospital in the Netherlands providing information for this study is the AMC in Amsterdam. At the request of the principal investigator of EuroSIDA, Prof. Peter Reiss, SHM collects data from the AMC in Amsterdam for EuroSIDA.

Publications in 2011 related to EuroSIDA include:

- *Estimating prevalence of accumulated HIV-1 drug resistance in a cohort of patients on antiretroviral therapy.* W Bannister, A Cozzi-Lepri, J Kjær, B Clotet, A Lazzarin, JP Viard, G Kronborg, D Duiculescu, M Beniowski, L Machala, A Phillips; the EuroSIDA study group. *J Antimicrob Chemother.2011 Apr;66(4):901-11. Epub 2011 Jan 31.*
- *A standardized algorithm for determining the underlying cause of death in HIV infection as AIDS or non-AIDS related: Results from the EuroSIDA study.* JD Kowalska, A Mocroft, B Ledergerber, E Florence, M Ristola, J Begovac, H Sambatakou, C Pedersen, JD Lundgren, and O Kirk; for the EuroSIDA study group. *HIV Clin Trials. 2011 Mar-Apr;12(2):109-17.*
- *Tuberculosis among HIV-positive patients across Europe: changes over time and risk factors.* A Kruk, W Bannister, D Podlekareva, N Chentsova, A Rakhmanova, A Horban, P Domingo, A Mocroft, J Lundgren, O Kirk; on behalf of the EuroSIDA study group. *AIDS. 2011 Jul 31;25(12):1505-13. Epub 2011 May 21.*
- *Vitamin D and clinical disease progression in HIV infection: results from the EuroSIDA study.* JP Viard, JC Souberbielle, O Kirk, J Reekie, B Knysz, M Losso, J Gatell, C Pedersen, JR Bogner, JD Lundgren, A Mocroft for the EuroSIDA Study Group. *AIDS. 2011 Jun 19;25(10):1305-1315.*
- *Predictors of having a resistance test following confirmed virological failure of cART: data from EuroSIDA.* ZV Fox, A Cozzi-Lepri, A d'Arminio Monforte, A Karlsson, AN Phillips, G Kronborg, J Kjaer, B Clotet, JD Lundgren for EuroSIDA. *Antiviral Therapy. 2011;16(5):781-5.*
- *Fatal and non-fatal AIDS and non-AIDS events in HIV-1 positive individuals with high CD4 counts according to viral load strata.* J Reekie, J Gatell, I Yust, E Bakowska, A Rakhmanova, M Losso, M Krasnov, P Francioli, J Kowalska, A Mocroft, for the EuroSIDA study group. *AIDS. 2011 Nov 28;25(18):2259-68. Epub 2011 Sep 13.*
- *A comparison of the long-term durability of nevirapine, efavirenz and lopinavir in routine clinical practise across Europe: A EuroSIDA study.* J Reekie, P Reiss, B Ledergerber, D Sedlacek, M Parczewski, J Gatell, C Katlama, G Fatkenhaeur, JD Lundgren, A Mocroft. *HIV Med. 2011 May;12(5):259-68. Epub 2010 Aug 31.*
- *A376S in the Connection Subdomain of HIV-1 Reverse Transcriptase Confers Increased Risk of Virological Failure to Nevirapine Therapy.* R Paredes, MC Puertas, W Bannister, M Kisic, A Cozzi-Lepri, C Pou, R Bellido, G Betancor, J Bogner, P Gargalianos, D Bánhegyi, B Clotet, J Lundgren, L Menéndez-Arias, J Martinez-Picado; The EuroSIDA Study Group. *J Infect Dis. 2011 Sep 1;204(5):741-52.*

- *Can Linear Regression Modeling Help Clinicians in the Interpretation of Genotypic Resistance Data? An Application to Derive a Lopinavir-Score.* A Cozzi-Lepri, MCF Prosperi, J Kjær, D Dunn, R Paredes, CA Sabin, JD Lundgren, AN Phillips, D Pillay, for the EuroSIDA and the United Kingdom CHIC/United Kingdom HDRD Studies. *PLoS One. 2011;6(11):e25665. Epub 2011 Nov 16.*
- *The rate of accumulation of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance in patients kept on a virologically failing regimen containing an NNRTI.* A Cozzi-Lepri, R Paredes, AN Phillips, B Clotet, J Kjaer, V Von Wyl, G Kronborg, A Castagna, Jr Bogner, JD Lundgren for EuroSIDA in EuroCoord. *HIV Med. 2012 Jan;13(1): 62-72. Epub 2011 Aug 17.*

HIV-CAUSAL

The HIV-CAUSAL (HIV Cohorts Analyzed Using Structural Approaches to Longitudinal data) collaboration is a multinational collaboration of prospective studies of HIV-infected individuals from six European countries and the United States. It aims to answer three main questions: when to start antiretroviral therapy, what antiretroviral regime to use initially, and when to switch to another regime. Because these questions are unlikely to be answered by a single study, there is need for a collaborative project. The HIV-CAUSAL collaboration pools data collected for clinical purposes within health care systems with few barriers to access in the populations they serve. The collaboration is designed to inform evidence-based guidelines and the planning of clinical trials. In addition, it will facilitate understanding and training in causal modelling across leading HIV observational research groups in the United States and Europe.

The HIV-CAUSAL collaboration published the following paper in 2011:

- *When to Initiate Combined Antiretroviral Therapy to Reduce Mortality and AIDS-Defining Illness in HIV-Infected Persons in Developed Countries: An Observational Study.* HIV-CAUSAL Collaboration, Cain LE, Logan R, Robins JM, Sterne JA, Sabin C, Bansi L, Justice A, Goulet J, van Sighem A, de Wolf F, Bucher HC, von Wyl V, Esteve A, Casabona J, del Amo J, Moreno S, Seng R, Meyer L, Perez-Hoyos S, Muga R, Lodi S, Lanoy E, Costagliola D, Hernan MA. *Ann Intern Med. 2011 Apr 19;154(8):509-515.*

HIV in Europe

HIV in Europe is a pan-European initiative initiated in Brussels in 2007. It provides a European platform for exchange and activities to improve early diagnosis and earlier care of HIV across Europe. The initiative is directed by an independent group of experts with representation from civil society, policy makers, health professionals and European public health institutions. The initiative has put the issue of earlier diagnosis of HIV on the political agenda and involved the different constituencies. Also, it has been able to initiate specific projects to enhance optimal testing and care. The overall objective of the initiative is to ensure that HIV-positive patients enter care earlier in the course of their infection than is currently the case and to study the decrease in the proportion of HIV-positive persons presenting late for care.

RDI

The HIV Resistance Response Database Initiative (RDI) is made up of a small research team based in the UK, an International Scientific Advisory Group, and a network of collaborators and supporters. The main activities of the RDI are: exploring the relationship between changes in the genetic code of HIV (genotype); exploring other clinical and laboratory factors and response to HIV drug therapy; and developing computational models for helping physicians and their patients to select the best combination of drugs for the individual.

Publications in 2011 relevant to RDI include:

- *The development of an expert system to predict virological response to HIV therapy as part of an on-line treatment support tool*. Revell AD, Wang D, Boyd MA, Emery S, Pozniak AL, De Wolf F, Harrigan PR, Montaner JS, Lane HC, Larder BA; on behalf of the RDI Study Group. *AIDS. 2011 Sep 24;25(15):1855-1863. Epub 2011 Jul 21.*
- *Clinical evaluation of the potential utility of computational modeling as an HIV treatment selection tool by physicians with considerable HIV experience*. Larder BA, Revell A, Mican JM, Agan BK, Harris M, Torti C, Izzo I, Metcalf JA, Rivera-Goba M, Marconi VC, Wang D, Coe D, Gazzard B, Montaner J, Lane HC, The HIV Resistance Response Database Initiative (RDI). *AIDS Patient Care STDS. 2011 Jan;25(1):29-36.*

Financial report

Income

Income for regular HIV monitoring activities in the Netherlands

Stichting HIV Monitoring (SHM) is recognized by the Dutch Ministry of Health, Welfare and Sport as an official health care institute with a structural subsidy (Health Subsidy Regulation, Chapter II Institute Grants).

The Governing Board established the 2011 budget on 12 October 2010 at € 2,871,571. On 14 December 2010, the Dutch Ministry of Health, Welfare and Sport approved the budget. The indexation for the wage-sensitive part of the budget was set by the Ministry of Health on 14 September 2011 at 3.11% (€ 68,799). The material costs were not indexed. The total budget for 2011 allocated by the Ministry of Health for the monitoring of HIV in the Netherlands and available to SHM was fixed at € 2,940,370.

As of 1 June 2010, 14,617 of the registered patients (14,451 adults and 166 children) were in active follow-up, which represents an increase of 5.58% compared to the number of patients in 2009. The increase in the number of patients in active follow-up was actually higher than that recorded, which is largely due to backlogs in the processing of data by some HIV treatment centres as per 1 June 2010.

From 2010, the budget for the costs of HIV monitoring in the Netherlands included the processing of the increased number of new patients. Prior to 2010, this was excluded from the budget at the request of the Ministry of Health, Welfare and Sport.

Income through projects related to HIV monitoring

The participation of SHM in international studies is of great significance for both individual patients and the quality of care. Individual registration and monitoring programs (such as SHM) are often unable to provide a timely answer to questions regarding co-morbidity and changes in mortality trends in large-scale HIV treatment. In order to save time and provide insights into the long-term effects of HIV treatment, bringing large data sets from different countries through collaboration together is necessary. During 2011, income of € 1,181,127 was obtained from the following four projects related to HIV monitoring:

1 **Amsterdam Cohort Studies:**

SHM has been responsible for governing and administering the Amsterdam Cohort Studies (ACS) since 2005. Since 1984, research has been carried out on the natural course of HIV infection and on the development of the epidemic with data and materials provided by HIV-infected persons and persons at high risk of contracting HIV. The Ministry of Health, Welfare and Sport subsidises the ACS via the National Institute for Public Health and the Environment (RIVM) to the amount of € 500,000 in 2011. The Academic Medical Centre (AMC) of the University of Amsterdam (UvA) and the Municipal Health Service (GGD) of Amsterdam remain available to carry out projects within the ACS. The Academic Medical Centre Utrecht (UMCU) also carries out projects

in which data and material from ACS participants is used. For such use, the UMCU pays a fee to the ACS, which amounted to € 57,505 in 2011. The GGD Amsterdam and the AMC each contribute to these studies by storing patient data and material.

The contribution from the Ministry of Health, Welfare and Sport and the UMCU are, in accordance with the budget, transferred by SHM to the GGD Amsterdam and the AMC. Sanquin Blood Supply Foundation receives a contribution via the AMC for the processing and storage of patient material (specifically, white blood cells). SHM does not invoice costs for the maintenance of the ACS.

2 **Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D):**

D:A:D is a large international collaboration between observational cohorts, with the aim of identifying early severe side effects of treatment with antiretrovirals. SHM is a major partner in D:A:D. SHM collects data on side effects in registered patients for the benefit of the D:A:D study. The validity of this data is subject to 100% quality control (in contrast to the usual 10%) through source-data verification. The participation of SHM is this study contributes significantly to a higher quality of data for monitoring HIV in the Netherlands. In 2011, SHM contributed for the twelfth time to the data merge and received € 503,346 in compensation for this from the Hvidovre University in Copenhagen, the organisation that leads the D:A:D study.

In 2011, SHM was granted € 110,477 from the Hvidovre University Hospital for the registration of specific D:A:D-related events. This grant was paid in full by SHM to the HIV treatment centres that report D:A:D-related events.

3 **EuroSIDA:**

SHM participates in the EuroSIDA study within a European-based context. The AMC participates on behalf of the Netherlands in EuroSIDA, a European clinical cohort, with SHM delivering the AMC's patient data to the cohort. EuroSIDA carries out comparative studies on the effect of the treatment of HIV among the participating European countries, including a focus on new EU member states,. For its participation in the EuroSIDA study group in 2011, SHM received compensation of € 2,360.

4 **Other projects:**

In 2011, SHM received a contribution of € 7,440 for its active participation in the following international projects: Antiretroviral Cohort Collaboration (ART-CC) and Collaboration of Observational HIV Epidemiological Research Europe (COHERE).

Expenditure

Four different types of expenses for 2011 are outlined below:

1 **Compensation to the HIV treatment centres for anonymous patient data collection and data entry:**

In 2011, in accordance with the approved budget, SHM compensated the HIV treatment centres in the amount of € 68.38 per patient. The compensation to the HIV treatment centres is based on the number of patients who were in active follow-up on 31 December 2010 and on the adoption of the budget set by the Ministry of Health, Welfare and Sport. HIV treatment centres with a backlog in data collection received less of the budgeted amount than centres without a backlog. In 2011, by request of a number of hospitals, SHM offered assistance in data collection. The personnel costs incurred by SHM for this service were then charged to the hospital in question.

The compensation per patient increased by 0.83% in 2011 compared to that in 2010 (€ 67.82 per patient in 2010 and € 67.10 in 2009). A number of treatment centres have transferred the role of data collection to SHM. The costs incurred by SHM for this service are subtracted from the compensation to these centres.

In total, SHM paid the HIV treatment centres € 186,478.83 in 2011 to cover the costs for sampling and storing patients' plasma.

2 **Personnel costs:**

Personnel costs were once again the largest expenditure for SHM during 2011. As per 31 December 2011, SHM had a total of 36 employees (28.5 fte). This number does not include the employees of HIV treatment centres responsible for carrying out data collection for which the HIV treatment centres receive compensation from SHM.

In the framework of the SHM's European collaborations, it has carried out activities for Eurocoord and the European Centre for Disease Control and Prevention (ECDC). The fees amounting to € 88,952 for these studies are used primarily as compensation for salary costs of HIV monitoring. No personnel have been appointed specifically for these studies, and work carried out in 2010 and 2011 was within the available capacity of SHM. The tasks performed in these projects will be expanded during 2012, and as result additional staff must be appointed.

3 **Material costs:**

In addition to staff expenses in 2011, there were structural costs made in relation to database licenses, maintenance of the national HIV monitoring database, data management and operations.

4 **Other:**
SHM has provided for doubtful debts totalling € 57,505 in relation to an ongoing dispute with the University Medical Center Utrecht and the Amsterdam Cohort Studies regarding the 2011 defined contribution.

Earmarked reserves

In 2005, money was set aside for the Host Genetics project. The project was developed in collaboration with the Academic Medical Centre of the University of Amsterdam. No expenses were incurred in 2011.

In 2007, € 2,000 was set aside for the first Netherlands Conference on HIV Pathogenesis, Prevention and Treatment (NCHIV). The conference has since been organised annually by SHM in collaboration with the Dutch AIDS Fund, the AMC-UvA (including the Laboratory for Viral Immune Pathogenesis [LVIP] of the Department of Experimental Immunology, the Department of Global Health, and the Amsterdam Institute for Global Health and Development [AIGHD]), the Centre for Infectious Disease Control at the National Institute for Public Health and the Environment (CIb-RIVM), Sanquin Blood Supply foundation and the Dutch Association of HIV-Treating Physicians (NVHB). The earmarked sum of € 2,000 was maintained in 2011.

The D:A:D study financial reserve has been created so that the European commitments to the study can be maintained.

Operating result

The operating result of the HIV monitoring activities shows that the total expenditure for 2011 remains within SHM's income, with a positive result of € 56,143. This is due to:

1 In 2011, for the second consecutive year, the SHM limited salary increases. In this manner, increased employer costs could be absorbed through the salary-related indexation of the subsidy received through the Ministry of Health, Welfare and Sport.

2 In 2011, the UWV (the Institute for Employee Insurance) paid € 45,016 as compensation for maternity leave. For these three employees, no temporary replacement employees were hired in relation to the specialised nature of their work.

3 SHM charged the salary costs arising from the organisation of the annual NCHIV to the NCHIV Foundation. This amounted to € 38,400 and was a reimbursement of work carried out in 2010 and 2011.

4 SHM has released € 3,885 from the previous year's reserves. A claim can no longer be made on these reserves.

5 SHM received € 8,336 in 2010 to compensate for salary expenses incurred in a project conducted in collaboration with Imperial College, London for the European Centre for Disease Control and Prevention (ECDC). As this income was not taken into account in the financial statements of 2010, it is now recognized as revenue in 2011.

6 The interest income for 2011 amounted to € 13,328. SHM conducts a very conservative but accurate treasury policy.

The bulk of the addition to SHM's general reserves, amounting to € 456,921, is from projects related to HIV monitoring.

Reserves

The total financial reserves of SHM (including continuity reserve, general reserve and earmarked reserves for investment) amounted to € 2,218,670 on 31 December 2011.

1 **Continuity reserve:**
The continuity reserves amounted to € 30,476 on 31 December 2011. This amount includes the 2011 result of HIV monitoring in the Netherlands. The continuity reserve is thus about 1% of the 2011 budget.

2 **General reserve:**
From 2002 through 2007, SHM built a general reserve of € 382,205. The continuity reserve and the general reserve are held in reserve to guarantee 12 months of salary payments.

3 **Earmarked reserves for investment, HIV-related projects:**
As per 31 December 2011, a total of € 1,805,989 has been reserved for HIV-related projects. SHM has committed to participating in these projects for three years. SHM's Governing Board will make further decisions about the amount of this reserve in the spring of 2012. Any decisions will be based partly on the advice of SHM's Advisory Board on new registration and monitoring proposals.

Continuity risks

SHM applies the rule that 25% of the annual turnover is to be kept in reserve to cover continuity risks for the registration and monitoring of HIV in the Netherlands. The reserve for the regular HIV registration and monitoring activities in 2011 equalled approximately 14% of the budget.

Balance sheet as of 31 December

	31-Dec-11 (€)	31-Dec-10 (€)
Assets		
Fixed assets		
Tangible fixed assets	6,026	12,704
Total fixed assets	**6,026**	**12,704**
Current assets		
Debtors and accrued assets	254,901	171,997
Cash	3,156,523	2,566,433
Total current assets	**3,411,424**	**2,738,430**
Total Assets	**3,417,450**	**2,751,134**
Liabilities		
Capital and reserves		
• Continuity reserve	30,476	-25,667
• General reserve	382,205	382,205
• Earmarked reserves for investment	1,805,989	1,349,067
Total reserves	**2,218,670**	**1,705,605**
Short-term liabilities		
Short-term liabilities and accrued expenses	1,198,780	1,045,529
Total short-term liabilities	**1,198,780**	**1,045,529**
Total liabilities	**3,417,450**	**2,751,134**

Profit and Loss Account

	2011 €)	2010 (€)
Profits		
Total subsidies	4,121,497	3,808,129
Other profits	90,177	9,900
Total net revenue	**4,211,674**	**3,818,029**
Operation costs		
Personnel expenses	1,870,860	1,805,316
Depreciation on tangible fixed assets	6,677	15,196
Other operation charges	425,945	360,266
Compensation HIV-treatment centres	754,838	630,328
Compensation D:A:D-events	110,477	95,620
Compensation Amsterdam Cohort Studies	557,505	553,088
Compensation NCHIV	14,706	11,500
Compensation ECDC 2011 project noting benefit to HIV monitoring administration	0	0
Total operation costs	**3,741,008**	**3,471,314**
Operating result	470,666	346,715
Financial income and expenses	42,398	31,361
Total operating result	**513,064**	**378,076**
Year Result	**513,064**	**378,076**

Composition SHM

Governing Board SHM

Name	Position	Affiliation
Dr. F.P. Kroon	Chairman	NVHB
Dr. J.S.A. Fennema	Secretary	GGD Nederland
Drs. A.J. Lamping	Treasurer	Zorgverzekeraars Nederland
Prof. R.A. Coutinho	Observer	RIVM
Drs. J.C.H.G. Arts	Member	NVZ (until 17 October 2011)
Drs. P.E. van der Meer	Member	NVZ (from 17 October 2011)
Dr. R.J.M. Hopstaken	Member	NFU
Dr. H.G.P.M. van Rooij	Member	HIV Vereniging Nederland (until 12 June 2011)
Dhr. L.M.J. Elsenburg	Member	HIV Vereniging Nederland (from 17 October 2011)
Prof. K. Stronks	Member	AMC-UvA
Drs. M.I. Verstappen	Member	AGIS

Advisory Board SHM

Name	Affiliation
Prof. J.M.A. Lange (Chairman)	AMC, Dept. of Global Health and AIGHD, Amsterdam
Prof. Sir R.M. Anderson	Imperial College, Faculty of Medicine, Dept. of Infectious Disease Epidemiology, London, UK
Prof. M. Egger	University of Bern, Switzerland / Bristol, UK
Dr. S.E. Geerlings	AMC, Dept. of Internal Medicine, Amsterdam
Prof. D.R. Kuritzkes	Brigham and Women's Hospital, Section of Retroviral Therapeutics, Boston, MA, USA
Dhr. C. Rümke	HIV Vereniging, Amsterdam
Prof. J. Schuitemaker	AMC, Dept. of Internal Medicine, Amsterdam

Working group SHM

Members

Name	Affiliation
Dr. M.E. van der Ende (Chairman)	Erasmus Medisch Centrum, Dept. of Internal Medicine, Rotterdam
Prof. C.A.B. Boucher	Erasmus Medisch Centrum, Dept. of Internal Medicine, Rotterdam
Dr. F.C.M. van Leth	KNCV Tuberculosis Foundation, The Hague
Dr. W.M.C. Mulder	HIV Vereniging Nederland
Prof. P. Reiss	AMC, Dept. of Internal Medicine, Amsterdam

Reviewers

Name	Affiliation
Dr. N.K.T. Back	AMC, Dept. of Human Retrovirology, Amsterdam
Prof. K. Brinkman	Onze Lieve Vrouwe Gasthuis, Dept. of Internal Medicine, Amsterdam
Prof. D.M. Burger	UMCN – St. Radboud, Dept. of Clinical Pharmacy, Nijmegen
Dr. E.C.J. Claas	LUMC, Clinical Virological Laboratory, Leiden
Prof. G.J.J. Doornum	Erasmus Medisch Centrum, Dept. of Virology, Rotterdam (Emeritaat)
Dr. S.P.M. Geelen	UMCU-WKZ, Dept. of Paediatrics, Utrecht
Prof. A.I.M. Hoepelman	UMCU, Dept. of Virology, Utrecht
Dr. S. Jurriaans	AMC, Dept. of Human Retrovirology, Amsterdam
Dr. J.R. Juttmann	St. Elisabeth Ziekenhuis, Dept. of Internal Medicine, Tilburg
Dr. P.P. Koopmans	UMCN – St. Radboud, Dept. of Internal Medicine, Nijmegen
Prof. A.C.M. Kroes	LUMC, Clinical Virological Laboratory, Leiden
Prof. T.W. Kuijpers	AMC, Dept. of Paediatrics, Amsterdam
Prof. J.M. Prins	AMC, Dept. of Internal Medicine, Amsterdam
Prof. P.H.M. Savelkoul	VU Medisch Centrum, Dept. of Medical Microbiology, Amsterdam
Dr. G. Schreij	Academisch Ziekenhuis, Dept. of Internal Medicine, Maastricht
Dr. R. Schuurman	UMCU, Dept. of Virology, Utrecht
Dr. H.G. Sprenger	Academisch Ziekenhuis, Dept. of Internal Medicine, Groningen
Dr. A.M.J. Wensing	UMCU, Dept. of Virology, Utrecht

Personnel SHM

Position	Name
Director	Prof. F. de Wolf MD
Research – Senior	Dr. D.O. Bezemer
	Drs. L.A.J. Gras
	Dr. A.I. van Sighem
	Dr. Ir. C. Smit
	Dr. R. Holman (from 1 January 2011)
Research – PhD students	Drs. A.M. Kesselring
	Drs. S. Zhang (until 31 December 2011)
Patient Data & Quality Control – Manager	Drs. S. Zaheri
Patient Data & Quality Control – Registration	R.F. Beard

Position	Name
Patient Data & Quality Control – Data collectors	M. van den Akker
	Y.M. Bakker
	M. Broekhoven-van Kruijne
	E.J. Claessen (from 7 March 2011)
	C.W.A.J. Deurloo-van Wanrooij
	L.G.M. de Groot-Berndsen
	C.R.E. Lodewijk
	B.M. Peeck
	Y.M.C. Ruijs-Tiggelman
	E.M. Tuijn-de Bruin
	D.P. Veenenberg-Benschop
	T.J. Woudstra
Patient Data & Quality Control – Data monitors	Drs. E. van der Beele
	R.A. van den Boogaard MSc (from 1 April 2011)
	Drs. S. Grivell
	Drs. M.M.J. Hillebregt
	Drs. A.M. Jansen
	V. Kimmel MSc
	Drs. B. Lascaris
	Drs. B. Slieker
Office, Administration, Communications – Manager	D. de Boer
Office	M.M.T. Koenen Bsc
	Drs. G.E. Scholte
Administration – Personnel & Administration	I.H.M. de Boer
	Drs. H.J.M. van Noort
Communications	L.J. Dolfing-Tompson BVSc

Scientific output 2011

In 2011, 9 requests were made for access to Stichting HIV Monitoring's (SHM's) cohort data. During the year, 41 papers including SHM cohort data were published in peer-reviewed journals. Furthermore, 39 abstracts were accepted for presentation at 9 meetings and conferences (24 posters and 16 oral presentations). All of these research projects, publications and presentations are listed on SHM's website, www.hiv-monitoring.nl.

Completed research projects

I06208 Long-term quality of life and self-reported symptoms among HIV-infected patients treated with highly active antiretroviral therapy

Sprangers MAG, Nieuwkerk PT.
Date of approval: December 2006

Publication in 2011: Self-Reported Symptoms Among HIV-Infected Patients on Highly Active Antiretroviral Therapy in the ATHENA Cohort in The Netherlands. de Boer M, Prins JM, Sprangers MAG, Smit C, Nieuwkerk PT. HIV Clin Trials 2011;12(3):161–170.

I0000 Role of host genetics in the clinical course of HIV infection

Schuitemaker H, van 't Wout A,
de Wolf F.
Date of approval: 14 February 2006

2011 progress summary:
The study by Fellay *et al* showed an association between genetic markers (SNPs) in HIV-1 infected patients and the viral load (VL)18 months after seroconversion (the so-called "set-point"). For example, a SNP in the HCP5 gene (rs2395029) and a SNP 35 kilobases upstream of the HLA-C gene region (-35HLA-C; rs9264942) have both been associated with a lower VL set-point[1]. In addition, it has been known that individuals heterozygous for a 32 base pair deletion in the CCR5 gene (CCR5Δ32) have a lower VL set-point. We have confirmed these associations in the homosexual participants of the Amsterdam Cohort Studies on HIV infection and AIDS with seroconversion prior to 1996[2]. Interestingly, a recent study in which the VL set-point was compared in seroconverters from before and after 2003 has shown that VL set-point levels have risen over the last decade of the HIV epidemic in the Netherlands[3]. This could imply that HIV has adapted to its host at the population level.

To test this hypothesis we used host genetic data in relation to viral load setpoint in the ACS and additionally selected over 700 patients in follow up at 1 of the 25 HIV treatment centers in the Netherlands with a known date of seroconversion (SC) and VL set-point. SC date was defined as the date of occurrence of symptoms of acute HIV infection and/or a first positive HIV test with a last negative HIV test less than 6 months prior. 20 of the 25 HIV treatment centers have approached patients for study participation.

As of December 31, 2011, 586 of the SHM selected patients have given informed consent and donated blood for DNA isolation. DNA of 355 patients with available VL data from 18-24 months after SC has subsequently been typed for the SNPs in HCP5 and -35HLA-C. In addition, the CCR5 genotype was determined. In the end, we compared the association between viral load set-point and HCP5 rs2395029, -35HLA-C rs9264942, and the CCR5wt/Δ32 genotype in HIV-1-infected individuals in the Netherlands who

had seroconverted between 1982 and 2002 (pre-2003 seroconverters, n=459) or between 2003 and 2009 (post-2003 seroconverters, n=231).

Viral load set-point in post-2003 seroconverters was significantly higher than in pre-2003 seroconverters ($P= 4.5x10^{-5}$). The minor alleles for HCP5 rs2395029, -35HLA-C rs9264942 and CCR5wt/Δ32 had a similar prevalence in both groups and were all individually associated with a significantly lower viral load set-point in pre-2003 seroconverters. In post-2003 seroconverters, this association was no longer observed for HCP5 rs2395029 and CCR5wt/Δ32. The association between viral load set-point and HCP5 rs2395029 had significantly changed over time while the change in impact of the CCR5wt/Δ32 genotype over calendar time was not independent from the other markers under study[4].

Our results suggest that the increase in VL set-point in the Netherlands indeed correlates with a decreased protective effect of certain genetic factors on VL set-point. This suggests that HIV variants are being selected at the population level that are less sensitive to genetic factors that protect against disease progression. This adaptation of HIV to the host over time is an important factor to take into account in the development of novel therapeutic strategies and vaccines.

In addition to the patients with known SC date and VL set-point, we have recruited patients with relatively low VL (viremic and elite controllers) as part of the International HIV Controller Study. In this study, strong associations with elite control of HIV-1 viremia was again restricted to SNPs on chromosome 6, more specifically in the region encoding HLA-B57[5].

References:
1 Fellay J *et al, Science* 2007, 317:944-947.
2 van Manen D *et al, AIDS* 2009, 23:19-28.
3 Gras L *et al, PloS ONE* 2009, 4:e7365
4 van Manen D *et al, AIDS* 2011, 25:2217-2226
5 Int. HIV Controllers Study, *Science* 2010,330:1551-1557.

Publication in 2011: Rising HIV-1 viral load set point at a population level coincides with a fading impact of host genetic factors on HIV-1 control. van Manen D, Gras L, Boeser-Nunnink BD, van Sighem AI, Maurer I, Mangas Ruiz MM, Harskamp AM, Steingrover R, Prins JM, de Wolf F, van 't Wout AB, Schuitemaker H; Dutch HIV monitoring foundation HIV-1 Host Genetics study. AIDS. 2011 Nov 28;25(18):2217-26.

I09071 The Impact of the presence of TAM's including revertants on the composition and the efficacy of a first line HAART regimen

van der Ende ME, el Barzouhi A, Schutten M, Rijnders BJA, e.a.

Progress: article in final version

Introduction: Since the introduction of HAART the epidemiology of Transmitted Drug Resistance (TDR) has changed significantly. Currently the most prevalent mutations in the Western European population are the TAM's. This study analyzes the influence of these single TAM's on efficacy of currently recommended first line HAART regimens.

Methods: A retrospective cohort analysis was conducted of Dutch HAART-naive Men who have Sex with Men (MSM) with a known sequence analysis of the HIV protease and reverse transcriptase, diagnosed with HIV between 2002 and 2008. Patients

were classified into 2 groups: MSM with a single mutation on one of the TAM positions and a major resistance mutation group, with one or more resistance mutations. Both groups were matched to MSM without any relevant mutations on 1) centre of attendance, 2) year of start HAART and 3) baseline HIV-RNA load. Rates of virological failure between the groups in the first 48 weeks after start of HAART were compared.

Results: Of the 1557 MSM diagnosed with HIV between 2002 and 2008, 115 (7.4%) patients had a single mutation on a TAM position. These index patients were matched to 199 control patients. The percentage starting on a regimen with a low GBR was 64% for the index patients and 70% for the control patients (p=0.27). Univariate hazard ratio for virological failure was 0.99 (95% CI 0.60-1.63, p=0.96) for the index patients versus their controls. In the group of index patients, patients who started on a low GBR regimen did not significantly fail more frequently than those who started on a high GBR regimen (hazard ratio 1.01, 95% CI 0.44-2.30, p=0.98). Virological failure in the index patients was also not significantly correlated with age, pretreatment viral load, CD4 cell count and Genetic Susceptibility Score (GSS). Patients in the mutation group did fail significantly more often than their controls: multivariate HR 2.11 (95% CI 1.14-3.90, p=0.017). Failure rates did not differ between the groups starting on a low versus a high genetic barrier regimen (GBR), but seemed to be related to the GSS, with a HR 1.97 (95% CI 0.84-4.66; p=0.12). Sixty-seven percent of the index patients switched a regimen during follow-up compared to 60% of the control patients (p=0.25). Four percent of the index patients changed regimen for reasons of virological failure compared to 4% patients of the control patients (P=0.92).

Conclusion: The presence of a transmitted single TAM mutation does not necessarily influence the efficacy of the preferred cART regimen (i.e. 2 NRTI and 1 NNRTI) and therefore should not be a definite reason to change this regimen. In presence of TDR it is of major importance to closely analyze the resistance profile and choose the individual drugs for the cART accordingly, based on Genetic Susceptibility Scores.

I11095 Quadruple versus triple antiretroviral therapy

Grijsen M.
Date of approval: 10 augustus 2011

Publication in 2011:
Quadruple antiretrovirale therapie heeft geen virologisch voordeel bij de behandeling van hiv-naïeve patiënten met een hoge plasma 'virale load'. Grijsen ML, Holman R, Gras LAJ, de Wolf F, Prins JM, namens de ATHENA nationale observationele cohort studie. Tijdschrift voor Infectieziekten vol 6 nr. 4 2011. (In Dutch)

Ongoing research projects

I07252 Study on sexual behaviour among HIV-infected homosexual men

Stolte I, Krol A, Prins M, van Eeden A, Groot M, Visser GB, Heijman T.
Date of approval: December 2007

Background: The incidence of sexual risk behaviour and sexually transmitted diseases among homosexual men has increased since the introduction of HAART. Especially HIV infected men have become an important target group for prevention. To be able to study the changes in sexual risk behaviour among these men we have as our objective to ask all HIV infected homosexual

men attending the Jan van Goyen medisch centrum in Amsterdam to participate in a behavioural cohort study. Our aim was to start including patients for this study in March 2008.

Methods: After giving informed consent, participants are asked to fill in a questionnaire on mainly sexual risk behaviour. We aim to repeat the questionnaire once a year to obtain insight in changes in behaviour over time.

Results: The inclusion of MSM at the JvG started in March 2009. By the end of 2009, 19 MSM were willing to participate in the ACS and answered and returned the questionnaire. By the end of 2011, this number remained the same and all these men are still followed according to our HOP protocol. This allows us to combine all data from all HIV positive participants followed at the JvG, resulting in a total population of 49 at the JvG and 79 else.

In 2010/11, data on sexual risk behaviour are used for a study investigating change in sexual risk behaviour before and after seroconversion in a period before and after cART. Results indicate that sexual risk behaviour decreases after seroconversion, but in the time period of cART this decrease is only temporary after 4 years it is almost the same as before seroconversion.

This study is accepted for publication in AIDS: Heijman T, Geskus RB, Davidovich U, Coutinho RA, Prins M, Stolte IG. Less decrease in risk behaviour from pre-HIV to post-HIV seroconversion among MSM in the combination antiretroviral therapy era compared with the pre-combination antiretroviral therapy era. AIDS. 2011 Dec 7. [Epub ahead of print]

Conclusion: Although the number of hiv-positive participants did not strongly increase as a result of our attempts, study results like those mentioned above stress the importance of longitudinal collection of behavioral data, also after seroconversion. Thus, we will continue to put efforts in maintaining these men in the HOP protocol.

I05513 HIV Resistance Response Database Initiative (RDI)

Revell A.
Date of approval: October 2005

The main activities of the RDI during 2011 were as follows:

Study 1: The development of new computational models to predict virological response to treatment without the use of genotype for use in resource-limited settings

Most of the RDI's experience has been with models that use HIV genotype as part of the dataset from which predictions of treatment response are made. Genotyping is currently not routinely available in most resource-limited settings. However, previous RDI studies have demonstrated that information about previous drug exposure contributes significantly to the accuracy of our models. It is possible that such information can act as a partial surrogate for genotype, since exposure to certain drugs in a failing regimen usually involves the development of certain 'signature mutations'.

A previous 'proof of principle' study established that models developed with large data sets, including treatment history information but not genotype data, can predict virological response with a high degree of accuracy. During 2011 we developed new 'no-

genotype' models using the latest, expanded datasets, tested these models with independent test sets and integrated the new models into the RDI's online, experimental treatment decision tool, HIV-TRePS.

Methods: The RDI identified approximately 16,000 treatment change episodes (TCEs) in its database that fit the criteria for the modeling. These data were largely from Europe, Canada, USA, Japan and Australia. A committee of 10 random forest models were trained to predict the probability of response to ART (<400 copies HIV RNA/ml) using the following data from 14,891 TCEs: viral load and CD4 count prior to change, treatment history, drugs in the new regimen, time to follow-up and follow-up viral load. The models were assessed during cross-validation, with an independent set of 800 TCEs from the RDI database, with 231 cases from RLS in sub-Saharan Africa and 30 from Romania. The area under the ROC curve (AUC) was the main outcome measure.

Results: The models achieved an AUC of 0·74-0·81 (accuracy of 68-76%) during cross validation, 0·76-0·77 (accuracy of 70-73%) with the 800 test TCEs and 0·58-0·65 (accuracy of 60-67%) with the TCEs from RLS. The models identified alternative, available drug regimens that were predicted to result in virological response for 63-100% of virological failures.

Conclusions: We developed computational models that predict virological response to ART without a genotype with comparable accuracy to genotyping with rules-based interpretation. These have the potential to help optimise antiretroviral therapy for patients in in countries with limited resources where genotyping is not generally available.

Integration of the models into the HIV-TRePS system:
Following the successful development of the 'no-genotype' models, the user interface of HIV-TRePS was amended to cater for cases without genotypes and the system reprogrammed to enable the installation of the new models. This option was launched in July 2011. Since its launch use of the no-genotype version of HIV-TRePS, primarily by users in resource-limited settings, has outstripped the use of the version that requires a genotype.

Annual importation of data from existing contributors:
In order to ensure that the RDI database and the data used to train its computational models reflect current clinical practice and include data generated during treatment including the latest drugs, it is essential that the RDI receives new data from its partners on a regular basis. A global programme of data updates and importation was undertaken during 2011. This involved:

1 Liaison with contributing centres
2 Analysis, sorting, ordering and editing prior to importation into the RDI database, to ensure compatibility and quality control
3 Importation of the data
4 Identification and resolution of any data inconsistencies
5 Extraction of treatment change episodes (TCEs) for use in subsequent computational modeling
6 Development of basic database statistics

Study 2: The development of new computational models that include the newest drugs and replacement of existing models to power HIV-TRePS

Background: The original computational models that were used to power the 'with genotype' version of HIV-TRePS cannot make predictions for maraviroc, raltegravir or tipranavir because of a lack of sufficient long-term follow-up data involving these drugs for model training and testing. Following the data collection initiative sufficient data were collected involving changes to regimens involving on raltegravir that new models could be developed that are able to predict responses to this drug.

Methods: 7,263 TCEs were identified that met all the criteria for the study. A committee of 5 random forest (RF) models was trained to predict the probability of virological response (follow-up viral load <50 copies HIV RNA/ml) from the following input variables: baseline viral load, baseline CD4 count, baseline genotype (62 mutations), drugs in the new regimen (18 drugs covered), six treatment history variables (selected on the basis of previous studies (zidovudine, lamivudine/emtracitabine, any NNRTIs, any protease inhibitors, enfuvirtide, raltegravir; and time to follow-up. A second committee of five RF models was developed with 18 individual treatment history variables. The models in each committee were developed using a 5x cross validation scheme. Their accuracy was assessed during cross validation and then with an independent set of 375 TCEs, in terms of the area under the receiver-operator characteristic curve (AUC).

Results: The RF models with six categorical treatment history variables achieved an average AUC of 0.815 (range 0.784-0.829) and the models with individual treatment history variables gave an average AUC of 0.820 (range 0.798-0.837). Overall accuracy followed the same pattern with the individual treatment history variable models being approximately 1% better on average. The AUC values for the TCEs containing raltegravir ranged from 0.66-0.76 for Committee 1 and 0.63 to 0.78 for Committee 2. When tested with the 375 independent TCEs, the two sets of models achieved averaged AUC values of 0.87 and 0.86. Overall accuracy figures were 89% and 87%. There were no significant differences in the performance of the two sets of models.

Discussion: The models achieved a consistent, high level of accuracy in predicting treatment responses. The differences between the models using the restricted set of treatment history variables and those using 18 individual drug history variables were minimal. The accuracy of the models for raltegravir TCEs was somewhat reduced compared with the overall performance, reflecting perhaps the relatively small number of raltegravir TCEs and/or the absence of genotype information relating to this inhibitor. The models are being used to power HIV-TRePS, the online aid to treatment selection.

Publications in 2011:

The development of an expert system to predict virological response to HIV therapy as part of an online treatment support tool. Revell AD, Wang D, Boyd MA, Emery S, Pozniak A, De Wolf F, Harrigan R, Montaner JSG, Lane HC, Larder BA on behalf of the RDI Study Group. AIDS 2011;25:1855-1863.

Clinical Evaluation of the Potential Utility of Computational Modeling as an HIV Treatment Selection Tool by Physicians with

Considerable HIV Experience. Larder BA, Revell AD, Mican J, Agan BK, Harris M, Torti C, Izzo I, Metcalf JA, Rivera-Goba M, Marconi VC, Wang D, Coe D, Gazzard B, Montaner J, and Lane HC. AIDS Patient Care and STDs 2011; 25(1):29-36.

I05511 Influence of HIV-1 co-receptor usage on the clinical course of infection under HAART and the outcome of antiretroviral therapy

Schuitemaker H, Brinkman K, van 't Wout A.
Date of approval: October 2005

Ongoing

I04034 The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D)

Reiss P.

The study continues to successfully follow currently more than 49,000 patients. The ATHENA cohort continues to rank amongst the top contributors to D:A:D. Funding for D:A:D which was through 2012 has been extended for another year, largely as a result of its success in meeting both its original aim of delineating the relationship between the use of antiretroviral drug classes and individual drugs and the risk of myocardial infarction, as well as with more recently added additional comorbidity endpoints which include end-stage renal disease, chronic severe liver disease and non-AIDS malignancies. Discussions are ongoing to extend the study beyond 2013. The results from the study regularly continue to inform and influence changes in international HIV treatment guidelines.
For additional information, please see www.cphiv.dk.

I08115 Proposal for collaboration and data exchange between HMF and RIVM for nation HIV/Aids surveillance and data transfer to ECDC in the context of EU obligations for reporting on HIV/Aids

op den Coul E, de Wolf F, van der Sande M, van Sighem A, Vlug J.

Ongoing

Publications in 2011: Sexually transmitted infections, including HIV, in the Netherlands in 2010. Vriend HJ, Koedijk FDH, van der Broek IVF, van Veen MG, Op de Coul ELM, van Sighem AI, Verheij RA, van der Sande MAB. RIVM rapport 210261009.

I08196 The effect of Radio Therapy on CD4 cell count in HIV-infected patients

Sankatsing SUC, Prins JM, Verbon A, Gras L.

Background: It came to our attention that the CD4 cell count of HIV-1 infected patients declined during radiotherapy. There is no mention of this phenomenon in the literature. We therefore did a pilot study in which patients with a solid tumour were identified in the SHM database. Retrospective data from 3 HIV centres (AMC, OLVG and Prinsengracht) were used for this pilot. The SHM database revealed 77 patients (between June 1991 and June 2007) with a solid tumour in these 3 centres. Examination of the medical records confirmed 68 patients with a solid tumour. Of these 68 patients 32 received radiotherapy (including 12 patients also treated with chemotherapy). From 23 patients a start and stop date of radiotherapy was known (including 8 patients also treated with chemotherapy). In 12 out of these 23 patients CD4 data before and after start of radiotherapy were available (3 also treated with chemotherapy). In

10 of these patients there was a significant and prolonged decrease of CD4 cells, which persisted even after stop of radiotherapy.

Because our pilot consisted of a small group of patients, we want to study this phenomenon in a larger population.

Hypothesis:
1 Radiotherapy is responsible for a decrease of the CD4 cell count in HIV-infected patients.
2 The speed of recovery of the CD4 cell count after stopping radiotherapy is independent of the CD4 cell count at start of radiotherapy.

Objective:
1 To study whether radiotherapy is responsible for a decline of CD4 cell count in HIV-1 infected patients.
2 To study the duration of the CD4 decline after stopping radiotherapy.
3 To study whether a relation exists between dosage of radiotherapy and the decline of CD4 cell counts and the duration of this decline.

Methods: This is a retrospective study. All patients with a solid tumour included in the SHM database will be included. The clinical records of these patients will be examined to check whether indeed a solid tumour was present and whether, when and how much radiotherapy was given. The change in CD4 cell counts and plasma HIV-1 RNA will be compared between patients who received radiotherapy and those who didn't.

Conclusion and results: 389 patients with a solid tumor were identified in the SHM database. Of 250 patients data was collected but 160 patients where excluded because they had no tumor or because of missing data. At this moment the data is being analysed and a manuscript is expected later this year.

I08109 Tenofovir-related renal toxicity in daily clinical practice: incidence and risk factors

Haverkort M., Van der Ende M.
Date of approval: 30 June 2008

The original aims of the project have been altered to take account of recent developments in the literature on HIV, tenofovir use and renal function and advice from clinicians. Work is ongoing to describe the most suitable methodology and statistical approach, given the data available. Work on the project will continue in 2012.

I09050 Contribution of multiple genetic variants, previously validated in genome-wide analyses, to acute coronary artery events in HIV-infected individuals – an international collaborative study

Schuitemaker H, Reiss P.
Date of approval : April 2009

HIV-infected individuals (HIV+) have an increased risk of coronary artery disease (CAD). Multiple genome-wide association studies (GWAS) of CAD have been conducted in the general population. A comprehensive analysis of the contribution of genetics, traditional risk and HIV-related factors has not been done in HIV+. For this purpose, the MAGNIFICENT Consortium was created, which includes 24 HIV observational cohorts distributed worldwide (USA=5, Europe=17, Argentina=1, Australia=1). There a centralized database containing clinical and laboratory documentation at Lausanne (Switzerland).

From the ATHENA cohort, DNA from 81 cases and 243 controls (3 controls per case) were shipped to Lausanne. In total, MAGNIFICENT has now enrolled 699 CAD cases and 1,962 matched controls. DNA samples from all cohorts have been centralized in Lausanne for genotyping. Genotyping has been performed with the Metabochip® (Illumina®/ Broad Institute), a custom array of 196,000 variants from gene regions associated with metabolic/cardiovascular traits in GWAS in the general population. The verification of the accuracy of the clinical data provided by the cohorts has been completed.

A preliminary analysis of the data has been accepted as a poster discussion in the 19th Conference of Retrovirus and Opportunistic Infections. The analysis of the genetic data is currently being finalized.

I08044 Primo SHM

Grijsen M, Welkers M.

Ongoing

I10042 The use of nevirapine dose escalation in patients who switch from efavirenz to nevirapine

Burger D, Blonk M, Wit F, Smit C, van Luin M, Gelinck L, Sprenger H, Koopmans P.
Date of approval: 11 May 2010

Progress of the research project was discussed at the SHM/NVHB research meeting on March 2nd 2011 and during the NVHB Midwintervergadering on January 13th 2012. The initial dosage of nevirapine after switching from efavirenz is not well documented or not collected in de cohort data from SHM. A pilot study was set up in UMC St Radboud and Rijnstate in order to develop a method to obtain these data about dose escalation from other sources. This method was expanded to the HIV treatment centers LUMC, St Elisabeth Hospital and Erasmus MC. After evaluation other treatment centers will be approached for participation. Obtaining and optimizing the cohort data by SHM is ongoing.

I010021 Uncovering Determinants of eco-evo Pathogen Dynamica with ABCmu

Ratman O.
Date of approval: 28 May 2011

Ongoing

I10053 Capture-recapture analysis to estimate the prevalence of HIV and tuberculosis in patients with tuberculosis and HIV-infection, respectively

van Leth F, Wit F, e.a.
Date of approval: 13 January 2011

A proper estimate of the prevalence of HIV-infection amongst tuberculosis patients will inform testing strategies for HIV and latent tuberculosis infection (LTBI) in this patient group and can guide preventive measures within the field of tuberculosis control.

The latest estimate used data from a small group of tuberculosis patients registered in 2001. However, during recent years, the population of tuberculosis patients has shifted towards a higher proportion of patients from countries with a high HIV prevalence, probably invalidating the 2001 estimate.

For a concise estimate of the prevalence of HIV-infection amongst tuberculosis patients, data from a complete and representative cohort of tuberculosis patients is required. The most efficient approach is to link the national database on tuber-

culosis and the national database on HIV-infection. A capture-recapture analysis on a linked dataset will provide a valid estimate on HIV prevalence amongst tuberculosis patients, and tuberculosis and LTBI prevalence amongst HIV-patients. It will also provide insights into the quality of reporting in both databases and guidance to improve the quality if needed.

The two national databases (NTR for tuberculosis, and SHM for HIV) were successfully merged by a combined effort from a data manager of SHM and a data manager from KNCV Tuberculosis Foundation. The PI received this database with anonymized data for further analysis. Initial analyses were performed which were shared within the study team. Currently the study team is in the process of interpreting the data and to define a strategy for dissemination of the results in a manuscript.

The data will be presented at an international workshop in Athens in March. The workshop has a strong methodological focus and discussions on the data will steer further work if needed.

A manuscript for submission is expected to be ready at the end of May 2012.

I10234 Effective and safe combinations of cART and chemotherapy in HIV-infected patients with malignant lymphoma

Burger D, e.a.
Date of approval: 14 December 2010

Ongoing

I10043 Therapeutic drug monitoring in children with HIV/AIDS in the Netherlands

Bastiaans D, Burger D, van Luin M, Hartwig N.
Date of approval: 1 November 2010

Ongoing

I10270 Predictors for Pneumocystis jirovecii pneumonia (PJP) during HAART era in ATHENA cohort.

van Lelyveld S, Hoepelman A, Gras L, Hermans S.
Date of approval: 24 March 2011

Currently the statistical analysis is ongoing. Timelines for the study – 1 May 2012: abstract; September 2012: first draft paper.

I11010 The effect of Maraviroc on serum markers

van der Pas V.
Date of approval: 9 February 2011

Background: With the increased life expectancy of human immunodeficiency virus (HIV) infected individuals due to highly active antiretroviral therapy (HAART) one of the potential long-term complications, end-stage liver disease, has become the third most important causes of death[1]. The majority of these deaths are due to hepatitis B (HBV) or hepatitis C (HCV) related decompensated liver cirrhosis[1]. A co-infection with HIV accelerates the development of liver fibrosis caused by these chronic viral hepatitides and increases the risk of developing cirrhosis[2,3]. The Hepatic Stellate Cells (HSC) appear to play an important role in this process. These cells express the chemokine receptor-5 (CCR5)[4]; recent research has suggested that inhibition of this receptor might slow down or even reverse the process of liver fibrosis[5].

Besides its function on the HCS, this receptor plays an important role in the fusion of a specific HIV-subgroup with its host cell. The entry inhibitor Maraviroc (MVC) specifically blocks the CCR5 receptor. This leads to the hypothesis that treatment with MVC in HIV-infected patients might slow down or reverse liver fibrosis in this group, by inhibiting the CCR5-receptor on HCS. The preferred method to asses this effect would be invasive liver biopsy. However, in this study we used the non-invasive makers APRI (AST to Platelets Ratio Index) and FIB-4 to asses a possible effect of MVC on the progression of liver fibrosis.

Methods: The database of the Stichting HIV Monitoring (SHM) was evaluated for HIV-infected individuals using MVC for 6 months or longer between January 2007 and February 2011. Of these patients the demographic, clinical and biochemical characteristics were obtained. Since Maraviroc is a relatively new drug, the expected number of patients was low and thus all HIV-positive individuals were included.

The degree of liver fibrosis was quantified by the APRI and the FIB-4. The APRI was calculated using the formula as described in the original article of Wai et al[6] with the AST's upper limit of normal (ULN) being 40 IU/L.

$$\text{APRI} = \frac{\text{AST (IU/L) / ULN x 100}}{\text{Platelet count}(\text{x } 10^9/\text{L})}$$

Liver fibrosis was classified into 3 classes with class 1 indicating that no clinically significant fibrosis is present, in class 2 the presence of fibrosis cannot be excluded and in class 3 were clinically significant fibrosis or cirrhosis is present. Cut-off values as described in the literature were used with class 1 $\leq$ 0,50, class 2 from 0,50 to 1,50 and class 3 > 1,50[6].

The FIB-4 was calculated using the formula described in the original article[7]. A cut-off value of $\leq$ 1,45 was used for class 1, class 2 from 1,45 to 3,25 and class 3 >3,2.

$$\text{FIB-4} = \frac{\text{Age [years] x AST [IU/L]}}{\text{Platelet count [x } 10^9/\text{L] x (ALT}^{1/2}\text{ [IU/L])}}$$

The APRI and the FIB-4 were calculated at 3 moments in time: a year before treatment with MVC was initiated (t=-1), when MVC was initiated (t=0) and a year thereafter (t=+1). Biochemistry from a 3 month period before or after the ideal moment in time was considered acceptable. Since the transaminases and the platelet counts are not specific for liver fibrosis, both markers were also calculated a year before treatment to assess the naturals fluctuations.

Results: Of the 143 patients using MVC during the study period, 95 satisfied the inclusion criteria. From only 27 patients sufficient biochemistry was available to calculate the APRI and the FIB-4 at all 3 moments in time. Four patients were HIV/HCV-coinfected, there were no HBV/HCV coinfections.

Spontaneous improvement of the APRI and FIB-4 markers occurred in a major part of the patients in the year before the start of MVC. This trend persisted in the first year of MVC-treatment (table 1). However, univariate analysis showed no significant effects of MVC-treatment on the non-invasive markers.

Concordance between the two invasive markers was calculated showing a kappa value of 0.053, indicating moderate concordance.

Table 1

	Year before start MVC		Start MVC		Year after start MVC	
	APRI	FIB-4	APRI	FIB-4	APRI	FIB-4
Class 1	16	10	20	15	24	17
Class 2	10	15	7	12	2	9
Class 3	1	2	0	0	1	1

Conclusion: Using the non-invasive serum markers APRI and FIB-4, no protective effect of MVC on the progression of liver fibrosis could be demonstrated in HIV-infected patients. However, the small sample size as well as the variability between the APRI and FIB-4, warrant further investigation on the effects of MVC on liver fibrosis in a larger subset of patients.

Decursus: As mentioned above, only in a limited number of patients enough laboratory data were available to calculate the non-invasive serum markers at three time points. Therefore, it is not possible to make concrete statements about the effect of MVC on the progression of liver fibrosis. We are currently evaluating on different methods to extend this number and thereby increasing the power of this study.

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I11072 Virologic response after initiation of triple-class antiretroviral therapy in patients with primary and chronic HIV infection
Grijsen M.
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Ongoing

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Richel O.
Date of approval: 2005

Ongoing

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